

Immunosuppression: Evolution in Practice and Trends, 1994–2004

H.-U. Meier-Kriesche^{a,*}, S. Li^b, R. W. G. Gruessner^c, J. J. Fung^d, R. T. Bustami^b, M. L. Barr^e and A. B. Leichtman^f

^a University of Florida, Gainesville, FL, USA

^b Scientific Registry of Transplant Recipients, University Renal Research and Education Association, Ann Arbor, MI, USA

^c University of Minnesota, Minneapolis, MN, USA

^d Cleveland Clinic, Cleveland, OH, USA

^e University of Southern California, Los Angeles, CA, USA

^f Scientific Registry of Transplant Recipients, University of Michigan, Ann Arbor, MI, USA

* Corresponding author: Herwig-Ulf Meier-Kriesche, MD, meierhu@medicine.ufl.edu

Over the last 10 years, there have been important changes in immunosuppression management and strategies for solid-organ transplantation, characterized by the use of new immunosuppressive agents and regimens. An organ-by-organ review of OPTN/SRTR data showed several important trends in immunosuppression practice. There is an increasing trend toward the use of induction therapy with antibodies, which was used for most kidney, pancreas after kidney (PAK), simultaneous pancreas-kidney (SPK) and pancreas transplant alone (PTA) recipients in 2004 (72–81%) and for approximately half of all intestine, heart and lung recipients. The highest usage of the tacrolimus/mycophenolate mofetil combination as discharge regimen was reported for SPK (72%) and PAK (64%) recipients. Maintenance of the original discharge regimen through the first 3 years following transplantation varied significantly by organ and drug. The usage of calcineurin inhibitors for maintenance therapy was characterized by a clear transition from cyclosporine to tacrolimus. Corticosteroids were administered to the majority of patients; however, steroid-avoidance and steroid-withdrawal protocols have become increasingly common. The percentage of patients treated for acute rejection during the first year following transplantation has continued to

decline, reaching 13% for those who received a kidney in 2003, 48% of which cases were treated with antibodies.

Key words: Acute rejection, immunosuppression, induction therapy, maintenance immunosuppression, SRTR, transplantation

Introduction

This article identifies trends that have evolved over the past decade in the use of immunosuppression for recipients of solid-organ transplants. These changes are well captured by the OPTN/SRTR data. A thorough organ-by-organ review of practices in the use of induction, maintenance and antirejection medications from 1995 to 2004 is provided. In addition to the trends in the employment of single immunosuppressive drugs, this article details the usage of combinations of these drugs (regimens) from 1999 to the present. Moreover, evolving trends in steroid-free immunosuppression and immunosuppressive maintenance minimization are described for the same time period. By way of summary, a final section in the article presents overall comparisons of immunosuppressive practices across various organ groups.

Since they were approved by the FDA in 1994, tacrolimus (Prograf[®], Astellas Pharma US, Deerfield, IL) and the improved formulation of cyclosporine, the cyclosporine microemulsion (Neoral[®], Novartis, East Hanover, NJ), and subsequently the generic version of microemulsions (Gengraf[™], Abbott/SangStat, Abbot Park, IL/Fremont, CA), have provided the foundation for maintenance immunosuppression regimens. However, over the last several years, the use of cyclosporine has been rapidly diminishing, giving way to use of tacrolimus. A similar transition has also been observed between the antimetabolites azathioprine (Imuran[®], GlaxoWellcome (New Zealand) Ltd., Auckland, New Zealand) and mycophenolate mofetil (Cellcept[®], Roche, Nutley, NJ), since the latter was approved by the FDA in 1995. Over the next several years, a number of new maintenance immunosuppressants were licensed by the FDA: sirolimus (Rapamune[®], Wyeth, Philadelphia, PA, 1999), and the new antibody preparations, rabbit antithymocyte globulin (Thymoglobulin[®], SangStat Medical Corp., Fremont, CA (1999), daclizumab (Zenapax[®], Roche, Nutley, NJ, 1999),

Note on sources: The articles in this report are based on the reference tables in the 2005 OPTN/SRTR Annual Report, which are not included in this publication. Many relevant data appear in the figures and table included here; other tables from the Annual Report that serve as the basis for this article include the following: Tables 1.9a and b, 5.6a–i, 6.6a–i, 7.6a–i, 8.6a–i, 9.6a–i, 10.6a–i, 11.6a–i, 12.6a–i, 13.6a–i, 15.4a and b, 15.5a and b and 15.4–15.15. All of these tables may be found online at <http://www.ustransplant.org>.

basiliximab (Simulect[®], Novartis, East Hanover, NJ, 2000). While the majority of transplant recipients received corticosteroids between 1995 and 2002, their use has somewhat declined during the last two years (2003–2004), reflecting the belief of some transplant physicians that some recently introduced immunosuppressive protocols will allow successful steroid avoidance or withdrawal.

Over the last several years, tacrolimus/mycophenolate mofetil has been the most commonly used discharge regimen for solid-organ transplant recipients, with the exception of intestine and heart recipients. During the same period, the combination of tacrolimus/mycophenolate mofetil was also the most frequently used maintenance regimen at 1 and 2 years posttransplant for recipients of most organs.

Antibody-based induction therapy continues to be administered to the majority of kidney and pancreas recipients and to roughly half of intestine and thoracic-organ recipients in 2004. However, its use in liver transplantation has been noticeably limited. The choice of antibody preparations employed indicates continuing transition from muromonab-CD3 (OKT3[®], Orthobiotech, Bridgewater, NJ) and horse antithymocyte globulin (ATGAM[®], Pharmacia & Upjohn, Kalamazoo, MI) to rabbit antithymocyte globulin (Thymoglobulin[®], SangStat Medical Corp.) and the monoclonal anti-IL-2-receptor antagonists daclizumab and basiliximab. During the prior 2 years, there has been an increasing usage of the anti-CD-52 monoclonal antibody alemtuzumab (Campath-1H[®], ILEX Pharmaceuticals, San Antonio, TX). In 2004, its use ranged from 2% for liver transplantation to 43% for pancreas transplantation.

Although corticosteroids are prescribed for the majority of patients, there is an increasing and notable trend toward steroid avoidance and minimization protocols, particularly in abdominal organ transplantation. Since 1999 there has been an increase in steroid withdrawal among first transplant solid-organ recipients. There was also a trend toward avoiding the use of steroids altogether (steroid avoidance), as detailed in the organ-specific sections below.

The incidence of acute rejection has declined over the last 10 years, and thus the percentages of patients requiring antirejection treatment have continued to decline. However, there has been an increase in the use of antibody induction for the prophylaxis of acute rejection during the first year following transplantation. This usage ranged from 18% of heart-lung recipients to 77% of pancreas recipients in 2004. This has largely reflected the increased utilization of rabbit antithymocyte globulin.

This article focuses on organ-specific discussions, including usage of antibody induction, maintenance immunosuppression, corticosteroids and the treatment of acute rejection. For consistency, we have used generic drug names

wherever possible. However, Table 1 indicates the corresponding drug class names and brand names, which are commonly employed in clinical practice and many of the data collection forms used to prepare the tables and figures of this report.

This article presents a snapshot of current immunosuppressive practices for transplantation of all organ groups. Some procedures are performed less frequently—particularly intestine, heart-lung and pancreas transplant alone—and the trends noted for these organ groups may reflect practices at the smaller number of centers where such procedures are concentrated.

Unless otherwise noted, the statistics in this article are drawn from the reference tables in the *2005 OPTN/SRTR Annual Report*. A companion article in this report, 'Analytical Methods and Database Design: Implications for Transplant Researchers, 2005,' explains the methods of data collection, organization and analysis that serve as the basis for this article (1). Additional detail on the methods of analysis employed herein may be found in the reference tables themselves or in the Technical Notes of the *OPTN/SRTR Annual Report*, both available online at <http://www.ustransplant.org>.

Kidney Transplantation

Induction immunosuppression for kidney transplantation

The use of induction immunosuppression for kidney transplantation continued to increase steadily through the decade (Figure 1). Currently 72% of kidney transplant recipients are receiving induction immunosuppression, compared to 46% in 1995. The administration of antithymocyte globulin (rabbit), the most commonly used induction agent, has increased—it is currently used for 37% of patients. In 2003, the first year that the usage for alemtuzumab was reported, it was used for 4% of patients; this practice nearly doubled in 2004 to 7%.

The overall use of induction therapy was fairly similar among different racial groups and, surprisingly, among groups with different panel reactive antibody (PRA) scores. Across maintenance treatment regimens there was a significant fluctuation in the use of induction immunosuppression, with nearly 80% of patients on sirolimus/mycophenolate mofetil receiving induction treatment, but only 53% of patients on cyclosporine/sirolimus receiving it.

Most of the patients (71%) on steroid-avoidance regimens between 2000 and 2004 received induction therapy. Antithymocyte globulin (rabbit), used for 40% of patients in steroid-avoidance protocols, was the most frequently used induction agent also in this group. Alemtuzumab was used more frequently for patients on steroid avoidance (10%), compared to other protocols.

Table 1: Immunosuppressive drug names in OPTN/SRTR data

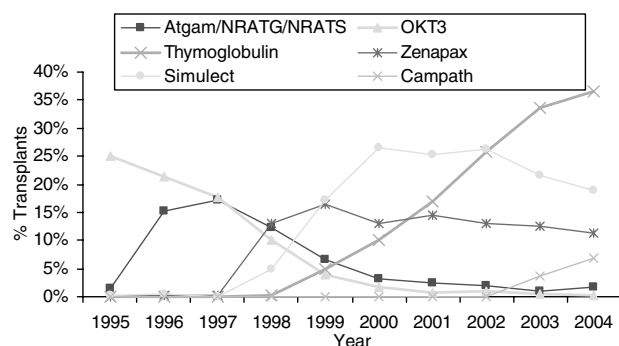
General class	Generic name	Brand name
Corticosteroids	Prednisone	Orasone, Deltasone
	Methylprednisolone	Solu-Medrol, A-methaPred, Medrol
	Dexamethasone	Decadron
Calcineurin inhibitors	Tacrolimus (or FK-506)	Prograf
	Cyclosporine (also cyclosporin A, CsA)	Sandimmune, Neoral; manufacturers of generic cyclosporine include SangStat (SangCya) ¹ , Abbott (Gengraf), Apotex, Bedford Eon Labs, Geneva, Ivax Pharms, Novex, Morton Grove, and Pliva
Antimetabolites	Azathioprine (or AZA)	Imuran
	Cyclophosphamide	Cytoxan, Neosar
	Mycophenolate mofetil (also MMF, RS61443)	CellCept
	Mycophenolic sodium (also ERL, mycophenolate acid)	Myfortic
	Methotrexate	Rheumatrex, Trexall
Polyclonal antibodies	Leflunomide (or LFL) ²	Arava
	Antithymocyte globulin (rabbit)	Thymoglobulin
Anti-CD3 monoclonal antibodies	Antithymocyte globulin (equine)	ATGAM
	Nashville rabbit antithymocyte globulin/serum (NRATG/NRATS)	
	Antilymphocyte globulin (ALG)	
	Muromonab-CD3	Orthoclone OKT3
Anti-CD52 monoclonal antibodies	Alemtuzumab ²	Campath-1H
Anti-IL-2 receptor monoclonal antibodies	Basiliximab	Simulect
	Daclizumab	Zenapax
TOR inhibitors	Sirolimus (or rapamycin)	Rapamune
	Everolimus (or RAD0001) ³	Certican (Phase III Trial)
Other	FTY720 ³	(Phase III Trial)

Note: For some immunosuppressants, the original data collection forms list brand names instead of generic names. As in the SRTR database, the figures in this article follow the terms on the data collection forms. However, the text refers to the drugs by their generic names when no additional generic alternatives exist.

¹Currently withdrawn from the market.

²Off label use.

³Currently only for investigational use.



Source: 2005 OPTN/SRTR Annual Report, Table 5.6a.

Figure 1: Immunosuppression agents used for induction in kidney transplantation, 1995–2004.

Maintenance immunosuppression before discharge for kidney transplantation

Calcineurin inhibitors were still the cornerstone of immunosuppression in kidney transplantation in 2004—93% of patients received them as part of their discharge regimen

(Figure 2). Tacrolimus is the calcineurin inhibitor of choice and its use continues to grow, with 72% of patients treated with tacrolimus at discharge versus only 21% with cyclosporine. The use of mycophenolate mofetil, the most frequently used antiproliferative agent, is also still increasing, with 81% of patients discharged on mycophenolate mofetil. Since a peak of 17% in 2001, the use of sirolimus (rapamycin) has declined. In 2004, only 12% of patients were discharged on regimens containing sirolimus.

Use of the combination of tacrolimus/mycophenolate mofetil continues to increase; it is the most frequently used discharge regimen (60%), followed by cyclosporine/mycophenolate mofetil, the use of which has continued to decline, reaching 16% in 2004 (Figure 3). Employment of the third most frequent regimen, tacrolimus/sirolimus, declined slightly to 5% in 2004. The use of the cyclosporine/sirolimus combination has continued to decline, with only 3% of patients being discharged on it in 2004. Use of the sirolimus/mycophenolate mofetil combination has remained under 1%.

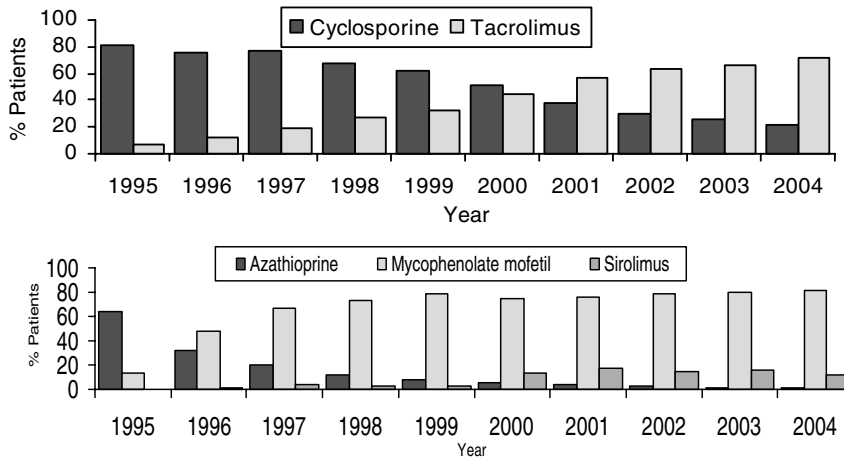


Figure 2: Trends in maintenance immunosuppression prior to discharge for kidney transplantation, 1995-2004.

Source: 2005 OPTN/SRTR Annual Report, Table 5.6e.

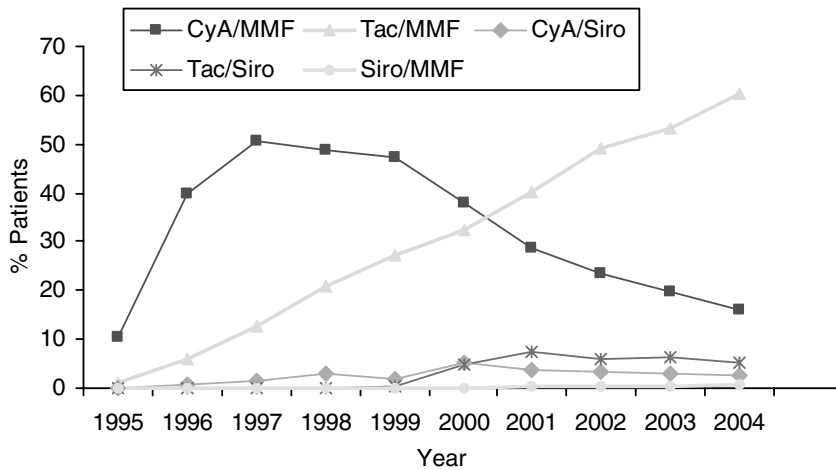


Figure 3: Trends in discharge immunosuppression regimens for kidney transplantation, 1995-2004.

Source: 2005 OPTN/SRTR Annual Report, Table 5.6d.

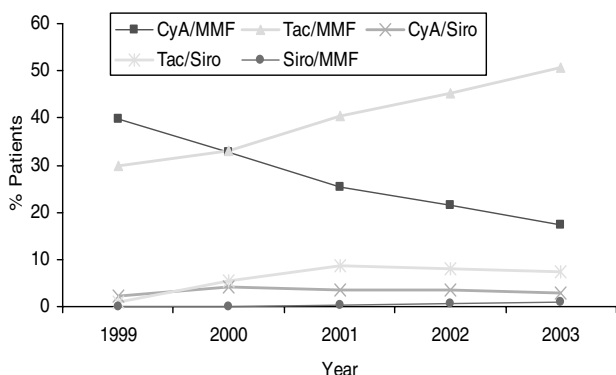
Maintenance immunosuppression 1 and 2 years following kidney transplantation

Tacrolimus/mycophenolate mofetil is also the most frequently used maintenance immunosuppression combination at 1 and 2 years following transplantation, and its prevalence for maintenance use has increased in recent years. At 1 year after transplantation in 2003, 51% of patients were receiving tacrolimus/mycophenolate mofetil, 17% were receiving cyclosporine/mycophenolate mofetil, 8% tacrolimus/sirolimus and 1% sirolimus/mycophenolate mofetil (Figure 4). Both the tacrolimus/sirolimus and the sirolimus/mycophenolate mofetil regimens were more prevalent at 1 and 2 years after transplant than at discharge, indicating a significant switch toward these combinations after transplant. Surprisingly, at 1 year about 7% and at 2 years about 2% of patients were receiving tacrolimus alone, compared to about 4% at discharge. All of these percentages refer to medication regimens regardless of steroids, meaning that most of the patients were on steroids in addition to the indicated regimens.

A minority of patients received only one drug for maintenance immunosuppression, but there has been an increase in patients on strict monotherapy at hospital discharge from 2% in 1999 to 4% in 2004 (SRTR analysis, May 2005). Most of these patients are either on steroids or on tacrolimus alone. The picture is similar at a year after transplant, with a small but steadily increasing number of patients on only one drug (3% in 2003) and more than half of these receiving only tacrolimus.

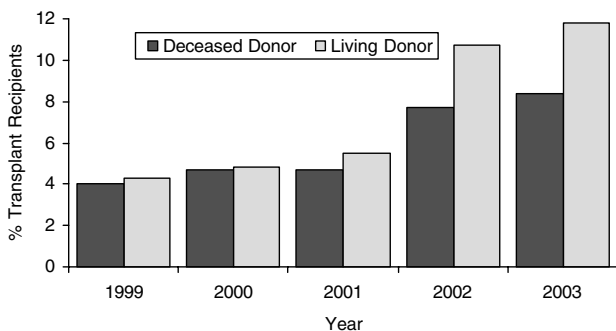
Steroid withdrawal and steroid avoidance for kidney transplantation

As seen in Figure 5, steroid withdrawal became increasingly established among recipients of a first kidney transplant between 1999 and 2003. In 1999, 4% of patients were taken off steroids by 1 year following transplantation, compared to 10% in 2003. At 2 years, a slightly higher proportion of patients who had been on steroids at discharge were no longer receiving them. Steroid withdrawal was slightly more common among living versus deceased donor transplants.



Source: 2005 OPTN/SRTR Annual Report, Table 5.6f.

Figure 4: Trends in immunosuppression maintenance regimens, 1 year posttransplant for kidney transplantation, 1999–2003.



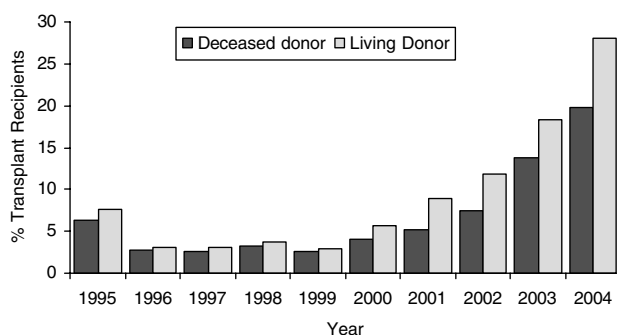
Source: 2005 OPTN/SRTR Annual Report, Tables 15.4a.2 and 15.4b.2.

Figure 5: Steroid-withdrawal rates at 1 year posttransplant for deceased donor and living donor kidney transplants, 1999–2003.

Currently, steroid avoidance is much more prevalent than steroid withdrawal, with 23% of all first transplants in 2004 discharged without steroids (Figure 6). The first significant numbers of steroid-avoidance protocols were seen in 2000, when 5% of patients were discharged without steroids; there has since been a steady increase in the prevalence of steroid-free regimens. Steroid-avoidance protocols are used more frequently for living donor transplant recipients (28% in 2004) than for recipients of deceased donor organs (20%).

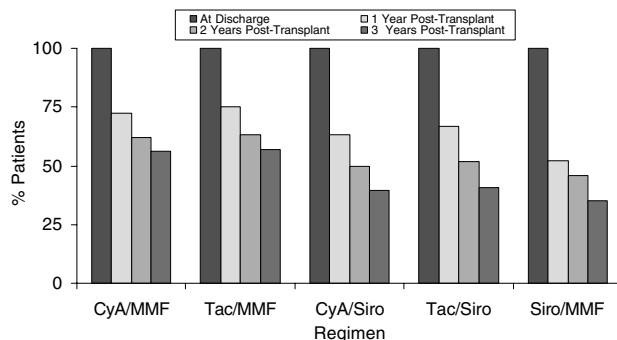
Maintenance regimen change and discontinuation for kidney transplantation

A surprisingly low percentage of patients continued their original immunosuppressive discharge regimen throughout the first 3 years following transplantation, as seen in Figure 7. Already at a year, a substantial number of patients were reported not to be on their original regimen. There was significant variability by immunosuppressive regimen. Among patients transplanted in 2001, most were still on



Source: 2005 OPTN/SRTR Annual Report, Tables 15.4a.1 and 15.4b.1.

Figure 6: Steroid-avoidance rates for deceased donor and living donor kidney transplants, 1995–2004.



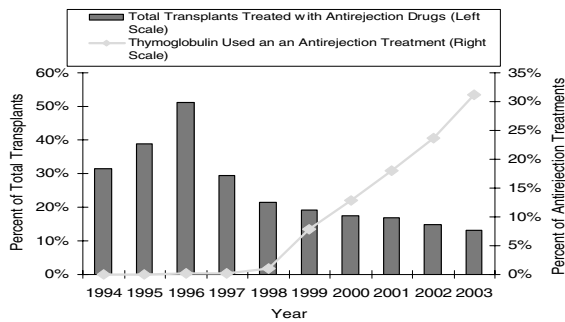
Source: 2005 OPTN/SRTR Annual Report, Table 5.6h.

Figure 7: Percentage of kidney transplant patients still on original discharge regimens at 1, 2 and 3 years posttransplant, for the five most common regimens in 2001.

their original tacrolimus/mycophenolate mofetil discharge therapy at both 1 (75%) and 3 years (57%) following transplantation. All sirolimus-based regimens showed high regimen change rates, particularly by 3 years after transplantation, with up to 65% of patients not on the original regimen in the sirolimus/mycophenolate mofetil group in 2001.

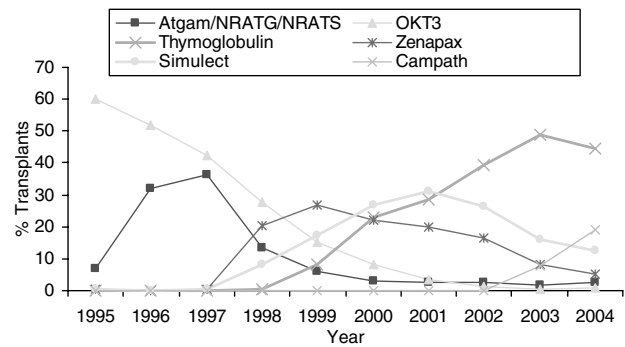
Antirejection treatment for kidney transplantation

The percentage of patients treated for acute rejection has continued to decrease. Only 13% of all patients who received a kidney in 2003 were reported to have been treated for acute rejection during the first year following transplantation (Figure 8). Among these acute rejection episodes, treatment with antibodies has increased—in 2003, 48% of patients requiring antirejection treatment received antibodies. The rise in antibody treatment largely reflects the increased use of antithymocyte globulin (rabbit) for antirejection (31% of antirejection treatments in 2003, up from 24% in 2002). Corticosteroids remain a principal element of rejection treatment even though their use declined slightly. In 2003, 72% of patients requiring antirejection treatment received steroids, down from 80% the previous year.



Source: 2005 OPTN/SRTR Annual Report, Table 5.6i.

Figure 8: Percentage of kidney transplants with antirejection treatments and thymoglobulin used as an antirejection treatment by year, 1994–2003.



Source: 2005 OPTN/SRTR Annual Report, Table 8.6a.

Figure 9: Immunosuppression agents used for induction in simultaneous kidney-pancreas transplantation, 1995–2004.

Pancreas Transplantation

Immunosuppressive practices and trends after pancreas transplants, in contrast to other solid-organ transplants, vary with the different recipient categories. It is well documented that pancreas allograft rejection rates are highest in nonuremic recipients of a pancreas transplant alone (PTA), next highest in posturemic recipients of a pancreas after kidney transplant (PAK) and lowest in uremic recipients of a simultaneous pancreas and kidney (SPK) (2,3). As a consequence, induction and maintenance regimens differ between the three recipient categories—comparisons are usually made between solitary pancreas transplants (PTA and PAK categories) versus combined pancreas and kidney transplants (SPK category). As shown in this analysis, immunosuppressive therapy after pancreas transplants continues to evolve; there appears to be a primary trend toward steroid avoidance, but avoidance of calcineurin inhibitors is also practiced.

Induction immunosuppression for pancreas transplantation

The use of antibody induction therapy remains higher for pancreas recipients than for recipients of any other solid organ; in 2004, the rate of such use reached over 80% in all three recipient categories. This rate is higher than it was 5 years ago, when 63% (PTA) to 67% (PAK) of pancreas recipients were given induction therapy.

Over the last 2–4 years, the most commonly used antibody administered after pancreas transplantation was antithymocyte globulin (rabbit), accounting for about half of all antibodies given for pancreas transplant induction therapy (Figure 9). Since 2003, the use of the monoclonal anti-CD-52-directed antibody alemtuzumab has been gaining acceptance; in 2004, it was the second most prevalent among all the three recipient categories. Alemtuzumab was given to 43% of PTA recipients (vs. 19% of SPK and PAK recipients). Monoclonal anti-IL-2 receptor antibodies

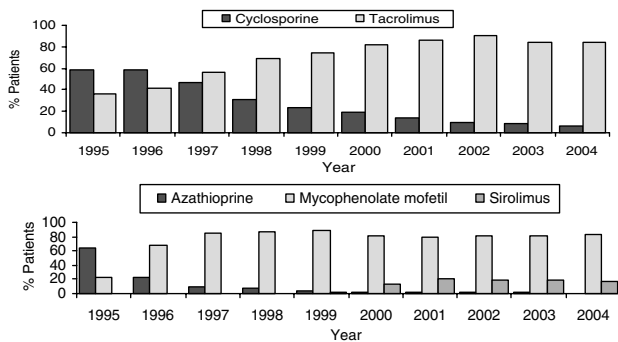
are the third most commonly used group, with basiliximab more common for SPK recipients and daclizumab more common for solitary pancreas transplant recipients during the last 5 years. Over time, the use of muromonab-CD3 and horse antithymocyte globulin/antilymphocyte globulin preparations has sharply decreased. They are now each used less than 3% of the time.

Another trend in induction therapy was noted in the 2005 report of the International Pancreas Transplant Registry (IPTR): Depleting and nondepleting agents are increasingly combined for induction therapy, least frequently for SPK recipients and most frequently for PTA recipients (2,3). The 2005 IPTR report also showed that graft survival in all the three recipient categories was higher when antibodies (vs. no antibodies) were used. Furthermore, for SPK recipients, the use of nondepleting antibodies, either alone or in combination, seems to be superior, when compared to the use of depleting antibodies alone or no induction therapy at all. For PAK recipients, graft survival rates were higher in those given depleting antibodies, either alone or in combination; for PTA recipients, no such differences were noted.

Of note, most recipients who received antithymocyte globulin (rabbit) or anti-CD-25 antibodies for induction therapy were placed on tacrolimus/mycophenolate mofetil maintenance therapy; in contrast, a higher percentage of patients on alemtuzumab for induction therapy were treated with either tacrolimus monotherapy or on sirolimus/mycophenolate mofetil for maintenance therapy.

Maintenance immunosuppression before discharge for pancreas transplantation

In essence, four basic trends in maintenance immunosuppression during the initial transplant hospitalization have been defined over time.



Source: 2005 OPTN/SRTR Annual Report, Table 8.6e.

Figure 10: Trends in maintenance immunosuppression prior to discharge for simultaneous kidney-pancreas transplantation, 1995–2004.

- (i) The use of steroids for maintenance immunosuppression has slowly but steadily decreased. In 2004, almost 24% of SPK recipients and almost 50% of PTA recipients were not given steroids (SRTR analysis, May 2005). Avoiding steroids appears to have become a major focus because of their deleterious side effects, particularly for patients with a long-standing history of diabetes mellitus.
- (ii) Among calcineurin inhibitors, tacrolimus remains the dominant agent (Figure 10). Since 2000, usage rates have been well over 80% in all three recipient categories. However, in 2004, though only among those undergoing PTA, a lower percentage of recipients (74%) were placed on tacrolimus. The use of cyclosporine and its different formulas has been marginalized. Its rate of use now ranges from 1% (PTA) to 9% (PAK).
- (iii) The antimetabolite of choice clearly is mycophenolate mofetil. In 2003 and 2004, 80–85% of all SPK and PAK recipients and 63–71% of all PTA recipients were placed on mycophenolate mofetil. Since 1999, fewer than 4% of recipients in all three categories were placed on azathioprine; in 2003 and 2004, fewer than 2% were.
- (iv) Since 2001, the use of rapamycin has remained fairly constant, ranging from 11% (in 2001 for PTA) to 22% (in 2001 for PAK).

Regarding combination therapy during the initial transplant hospitalization, the combination of tacrolimus and mycophenolate mofetil has been most common, accounting for 60–70% of all treatment regimens since 1999 for SPK and PAK recipients. Only in the PTA category, since 2001, have fewer than 60% of recipients been placed on tacrolimus/mycophenolate mofetil; in contrast, the percentage of tacrolimus monotherapy was highest for PTA recipients (10% in 2004). The second most frequently used combination in 2003 and 2004 was tacrolimus/rapamycin, accounting for 4–15% of protocols in each of the three recipient categories. Since 2001, cyclosporine-based com-

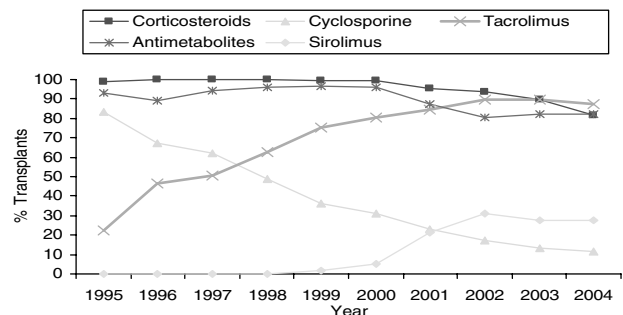
ination therapy (with mycophenolate mofetil, azathioprine or sirolimus) has been used in fewer than 10% of all regimens in all the three categories.

Calcineurin inhibitor-free protocols during the initial transplant hospitalization remain uncommon. The use of rapamycin/mycophenolate mofetil increased only in the PAK and SPK categories in 2003 and 2004, accounting for 2–7% of all combination regimens; its rate of use in the PTA category was less than 1%. Interestingly, in the PTA and PAK categories, the use of other protocols—such as the calcineurin inhibitor- and steroid-free alemtuzumab-mycophenolate mofetil-based protocol used at the University of Minnesota (4)—has increased; in 2004, these ‘other’ protocols accounted for 22% of therapy in the PTA category, 10% in the PAK category and 9% in the SPK category.

Maintenance immunosuppression 1 and 2 years following pancreas transplantation

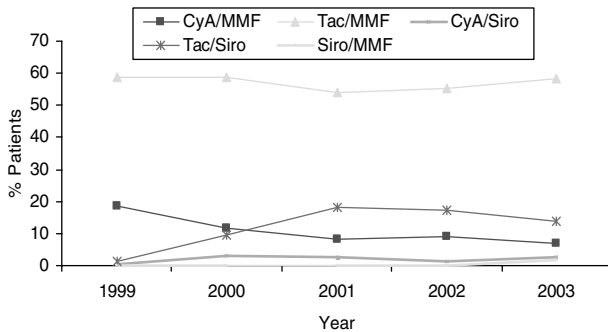
The trends in maintenance immunosuppression within the first year following transplantation have been similar to the trends during the initial transplant hospitalization (Figure 11):

- (i) Attempts at steroid avoidance began in 2003, when about 20% of SPK and PAK recipients and about 40% of PTA recipients were receiving steroid-free regimens. These numbers are slightly lower than during the initial transplant hospitalization, indicating that some recipients were administered steroids later on.
- (ii) Beginning in the mid-1990s, tacrolimus has been the most common calcineurin inhibitor, even at the first year following transplantation. In 2003, 74% (PTA), 76% (PAK) and 82% (SPK) of recipients were maintained on tacrolimus at 1 year following transplantation; the percentage of cyclosporine-based maintenance immunosuppression has decreased to about 10% for



Source: 2005 OPTN/SRTR Annual Report, Table 8.6g.

Figure 11: Immunosuppression agents used for maintenance between discharge and 1 year posttransplant in simultaneous kidney-pancreas transplantation, 1994–2003.



Source: 2005 OPTN/SRTR Annual Report, Table 8.6f.

Figure 12: Trends in immunosuppression maintenance regimens, 1 year posttransplant for simultaneous kidney-pancreas transplantation, 1999–2003.

SPK, 8% for PAK recipients and 8% for PTA recipients (Figure 12).

- (iii) Among antimetabolites, mycophenolate mofetil is most commonly used for maintenance. In 2002 and 2003, about 80% of PAK and SPK recipients were receiving mycophenolate mofetil at 1 year after transplantation; only for PTA recipients was the percentage lower (59% in 2003). Since 2001, $\leq 3\%$ of the recipients in all the three categories were given azathioprine.
- (iv) The use of rapamycin appears to have increased within the first year following transplantation (vs. the initial transplant hospitalization). In 2002 and 2003, 25–32% of all recipients were receiving rapamycin, about 10% more than during the initial transplant hospitalization. This trend toward greater usage of rapamycin after the transplantation may be explained by concern over a higher incidence of rapamycin-associated wound complications immediately following transplantation.

The most common combination therapy for the first year in all the three recipient categories is now tacrolimus/mycophenolate mofetil. Since 2000, it was given to 55–60% of SPK and PAK recipients. Only in the PTA category was a decrease in this combination’s use noted, in both 2002 (48%) and 2003 (30%). The second most common combination protocol was tacrolimus/rapamycin, given to 15–20% of all recipients in 2002 and 2003. Only in PTA categories was the administration of ‘other’ protocols prominent (18% PTA) in 2002 and 2003. This finding may also reflect the increased use of alemtuzumab/mycophenolate mofetil-based protocols that are free of both calcineurin inhibitors and steroids. Since 1999, cyclosporine-based immunosuppression has accounted for less than 10% of maintenance therapy (highest in the SPK category). In 2003, tacrolimus monotherapy was used for 2–3% of SPK and PAK recipients and up to 17% of PTA recipients. The calcineurin inhibitor-free rapamycin/mycophenolate mofetil protocol saw a slight increase in 2003 (2% SPK, 1% PAK

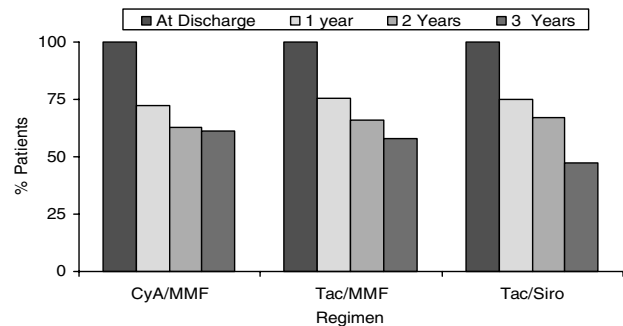
and PTA). Over time, the use of tacrolimus/rapamycin (vs. tacrolimus/mycophenolate mofetil) increased. In the second year following transplantation, about 17–20% of recipients in all the three categories received tacrolimus/rapamycin (vs. 55% on tacrolimus/mycophenolate mofetil). This change may reflect tacrolimus/mycophenolate mofetil-associated gastrointestinal problems. In the second year following transplantation, $\leq 2\%$ of all protocols were rapamycin/mycophenolate mofetil (calcineurin inhibitor-free).

Outcome by maintenance regimen in pancreas transplantation

According to the 2005 IPTR report, the 1-year pancreas graft survival rates for 2000–2004, for recipients of primary deceased donor pancreas transplants who were given anti-T-cell induction therapy and tacrolimus/mycophenolate mofetil for maintenance therapy, were as follows: 88% for SPK recipients, 83% for PAK recipients and 80% for PTA recipients. If tacrolimus/rapamycin was instead used for maintenance therapy, the rates were as follows: 87% for SPK recipients and 83% for both PAK and PTA recipients. The outcomes with either of these two maintenance protocols were similar. Multivariate models showed a highly significant reduction in early and late pancreas graft failure rates with tacrolimus-mycophenolate mofetil. Independently, the use of rapamycin decreased the hazard ratios for pancreas graft failure (3).

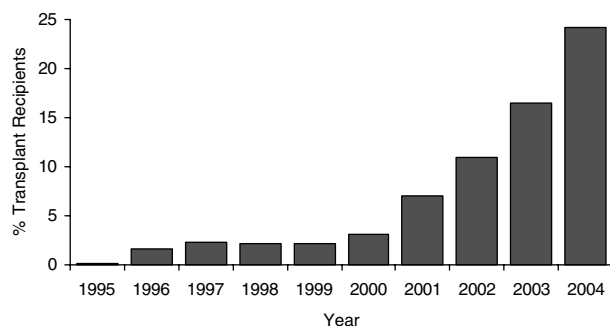
Maintenance regimen change and discontinuation for pancreas transplantation

A relatively low percentage of recipients in all three categories continued on their original immunosuppressive discharge protocol throughout their first 3 years following transplantation. The highest rate of regimen change occurred within the first year, but modifications continued throughout the second and third year. Figure 13 shows the rates of discontinuation for the three regimens most commonly used at discharge. Of all



Source: 2005 OPTN/SRTR Annual Report, Table 8.6h.

Figure 13: Percentage of simultaneous kidney-pancreas transplant patients still on original discharge regimen at 1, 2 and 3 years posttransplant, for the three most common regimens in 2001.



Source: SRTR analysis, May 2005.

Figure 14: Total steroid-avoidance rates at discharge for simultaneous kidney-pancreas transplants, 1995–2004.

recipients in the three categories who were initially placed on a regimen of tacrolimus/mycophenolate mofetil (the most common protocol) in 2001, only about 40–60% remained on it 3 years later. Of all recipients on tacrolimus/rapamycin, only 33% (PTA) remained on it 3 years later. Of note, the relatively small fraction of recipients on rapamycin/mycophenolate mofetil (calcineurin inhibitor-free) at the time of their initial transplant hospitalization was similar to that seen 3 years later.

Steroid withdrawal and steroid avoidance for pancreas transplantation

Rates of steroid withdrawal and steroid avoidance (Figure 14) following pancreas transplantation have both been rising since 1999. In 2004 (vs. 2000), 49% (vs. 17%) of PTA recipients and 24% (vs. 3%) of SPK recipients were on a steroid-avoidance regimen. The steroid-withdrawal rates at 1 and 2 years following transplantation have remained stable (at about 10%) for SPK recipients; this rate represents a clear increase from 1998 (<3%). For PTA recipients, in 2003 and 2004, the steroid-withdrawal rates were only slightly higher than those of SPK recipients. In general, steroid avoidance has been more popular than steroid withdrawal for pancreas recipients.

Regarding induction therapy, steroid-avoidance protocols were more commonly used if patients were given antithymocyte globulin (rabbit) or alemtuzumab for induction, and least commonly if they were given anti-CD-25 antibodies or no antibodies at all.

Minimization of immunosuppression (one-drug regimens) for pancreas transplantation

In general, minimization of immunosuppression to only one drug for maintenance has been infrequent among SPK recipients, but more common for PAK and PTA recipients. Since 1998, the percentage of SPK recipients receiving only one drug at the time of their hospital discharge and within the first 3 years following transplantation ranged from 0.4% to 6.4%; the most commonly used drug for monotherapy in 2004 was tacrolimus ($\geq 50\%$), followed by

mycophenolate mofetil and rapamycin (SRTR analysis, May 2005).

Up to 11% of PAK recipients were on only one drug at discharge, but the percentage decreased within the first 2 years posttransplant (down to 4%), only to increase again in the third posttransplant year (up to 12%). For PAK recipients, mycophenolate mofetil was the most commonly used drug for monotherapy (SRTR analysis, May 2005).

For PTA recipients, an increase in monotherapy during the initial transplant hospitalization was noted between 2000 (15%) and 2004 (33%) (SRTR analysis, May 2005). Over time, monotherapy was not sustained, and by the third year, no more than 6% remained on monotherapy. Mycophenolate mofetil was the most commonly used drug for monotherapy during the initial transplant hospitalization and in the third year following transplantation, but tacrolimus was the most commonly used drug in the first and second year.

Antirejection treatment for pancreas transplantation

Antibodies are used for antirejection treatment more frequently for pancreas recipients than for recipients of any other solid organ. In 2002 and 2003, more than 50% of all pancreas recipients requiring antirejection treatment were placed on antibodies. Since 1999, the rates of antibody use for antirejection treatment have been highest for PTA recipients (up to 90% in 2000) and lowest for SPK recipients (as low as 32% in 2001). The most commonly used antibody for antirejection treatment since 2001 has been antithymocyte globulin (rabbit), followed by muromonab-CD3, which was the most commonly used antirejection antibody from 1994 through 2000 (Figure 15). Alemtuzumab has emerged as another potent antirejection agent, particularly after solitary pancreas transplants. In 2003, for PTA and PAK recipients, alemtuzumab was already the second most commonly used antibody. Anti-IL-2 receptor monoclonal antibodies (basiliximab, daclizumab) accounted for about 10% of all antirejection treatments in 2003.

Steroids remain another cornerstone of antirejection treatment, given in about 80% of all rejection episodes. Their use is highest for PTA recipients (as high as 90% in 2001). In 2003, only 70% of SPK and PAK recipients with rejection were given steroid treatment. It remains to be seen whether steroids will be used less frequently when, for example, alemtuzumab is administered for antirejection treatment.

In general, the number of rejection episodes has declined since the late 1990s, presumably because of the introduction of both tacrolimus and mycophenolate mofetil in the mid-1990s. More efficient maintenance immunosuppression has lessened the need for antirejection treatment.

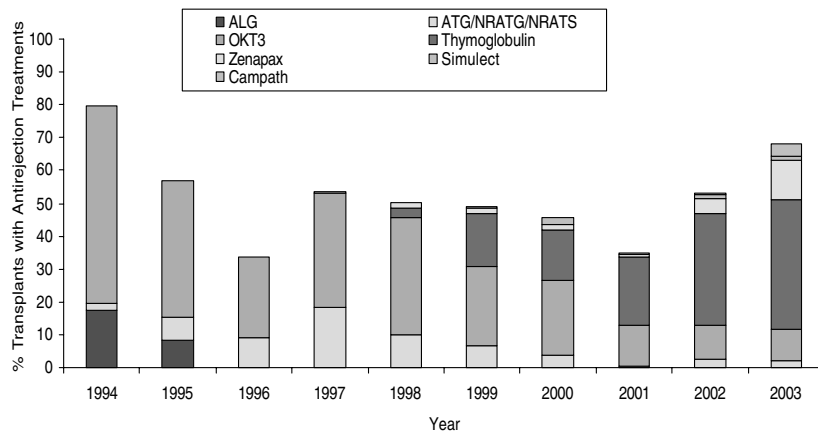
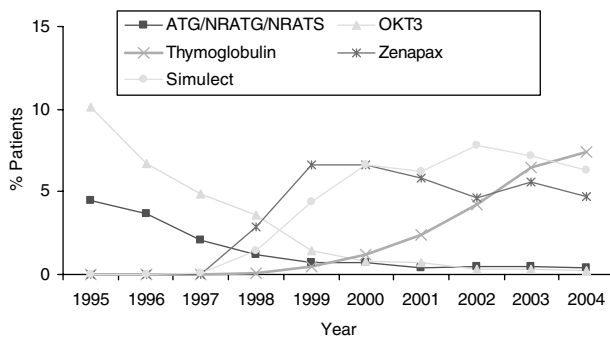


Figure 15: Trends in antibody therapy for rejection episodes in first year following simultaneous kidney-pancreas transplantation, 1994-2003.

Source: 2005 OPTN/SRTR Annual Report, Table 8.6i.



Source: 2005 OPTN/SRTR Annual Report, Table 9.6a.

Figure 16: Trends in induction immunosuppression for liver transplantation, 1995-2004.

Liver Transplantation

Induction immunosuppression for liver transplantation

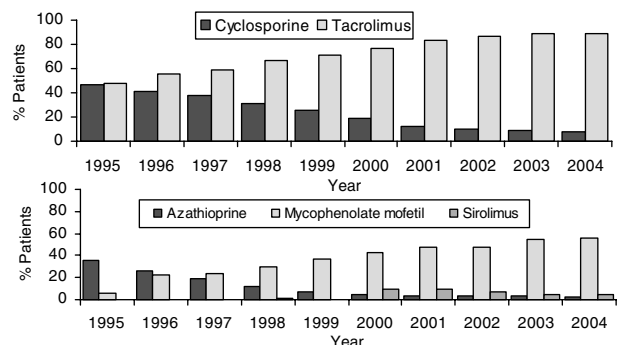
In contrast to all other solid-organ transplantation, the use of induction antibody preparations in liver transplantation remains relatively uncommon. As shown in Figure 16, the overall use of induction immunosuppression for liver recipients during 2003 and 2004 was 21%; the rate has increased steadily since 1997, when it was 7%. This rise in induction has been ascribed to an increase in calcineurin inhibitor avoidance in the early posttransplant period to avoid aggravation of renal dysfunction (a response to the higher prevalence of high MELD score patients with renal dysfunction), and to increased use associated with protocols to reduce early corticosteroid use (5), as well as to achieve early calcineurin inhibitor monotherapy (6).

The trend of induction antibody selection continues to favor the class of anti-IL-2 receptor alpha chain monoclonal antibodies (basiliximab and daclizumab), which make up a total of 11% overall use. Within this class, basiliximab use (6% overall) is slightly more common than is daclizumab (5%

overall). The use of rabbit antithymocyte globulin for induction was 7% of all liver transplant recipients. The long-term impact of alemtuzumab for liver recipients has not been defined and the FDA has not approved its use for organ transplantation; nevertheless, alemtuzumab was used in 2% of all induction following liver transplantation in 2004, twice what it was the previous year (7).

Maintenance immunosuppression before discharge for liver transplantation

The use of maintenance immunosuppression continues to favor the use of therapy based on calcineurin inhibitors. With the length of hospital stays after liver transplantation gradually falling to 8-15 days (8), and the impact of induction antibody use with delayed initiation of calcineurin inhibitors, the correlation of maintenance immunosuppressive therapy at the time of discharge with long-term outcomes has become increasingly difficult to determine. Nevertheless, the use of calcineurin inhibitors was reported in 97% of patients discharged from the hospital after liver transplantation in 2003-2004, as seen in Figure 17, with tacrolimus continuing to make up the



Source: 2005 OPTN/SRTR Annual Report, Table 9.6e.

Figure 17: Trends in maintenance immunosuppression prior to discharge for liver transplantation, 1995-2004.

largest proportion of calcineurin inhibitor use (89% of recipients) compared to all the cyclosporine preparations (8% of recipients). Use of antimetabolite therapy (mycophenolate mofetil or azathioprine) at the time of discharge was reported for 58% of all liver transplant recipients, and a recent study has suggested that the combination of mycophenolate mofetil and a calcineurin inhibitor may improve long-term outcomes, as compared to a calcineurin inhibitor alone (9). Sirolimus use at the time of discharge was noted for only 5% of liver transplants in 2003 and 2004.

Corticosteroid avoidance was stable at 5–8% until 1999, with the rates increasing to 20% in 2004. Avoiding corticosteroids has been postulated to be beneficial in reducing the impact of hepatitis C virus (HCV) recurrence in liver transplantation. However, analysis of steroid avoidance by listing diagnosis revealed that the increase in steroid avoidance was similar between the HCV-positive and -negative liver transplant recipients.

It has also been proposed that mycophenolate mofetil use for liver recipients transplanted for HCV may diminish HCV recurrence, due to its potent effects against other flaviviruses *in vitro* (10), although clinical studies have not consistently confirmed this (11). The use of mycophenolate mofetil has gradually increased since its introduction in 1995. Currently, a slightly larger number of HCV-positive patients receive mycophenolate mofetil than do HCV-negative patients (59% HCV+ vs. 55% HCV–) (SRTR analysis, May 2005). Confirmation of whether the practice of steroid avoidance and mycophenolate mofetil use in HCV patients is truly associated with improved clinical outcomes is pending the results of ongoing clinical trials examining the long-term outcomes of this approach (12).

Maintenance immunosuppression 1 and 2 years following liver transplantation

The pattern of immunosuppressive drug use changes in the years following liver transplantation. Withdrawal or elimination of corticosteroids early in the posttransplant period has been suggested as a means to avoid adverse effects related to corticosteroid use. Thus, the long-term steroid-free regimens have been widely touted; the OPTN/SRTR data reveal that corticosteroid administration indeed decreases over time. Of the approximately 80% of deceased donor liver transplant recipients discharged on corticosteroids, only 49% are still using them by the end of the first year after transplantation and 33% 2 years after transplantation.

Calcineurin inhibition is still the most prevalent baseline immunosuppression at 1 year after transplantation, when 93% of liver recipients are receiving a calcineurin inhibitor, with 84% tacrolimus and 9% cyclosporine. Cyclosporine antimetabolite use decreases at 1 year following transplantation (55%, compared to 58% at the time of discharge),

again with mycophenolate mofetil being the predominant agent (52%, vs. 3% for azathioprine). This decreased use of mycophenolate mofetil from the time of discharge to the 1 year posttransplant mark is consistent with single-center reports that report intolerance (13) or unknown long-term cost-benefit assessment (14). Sirolimus administration is 12% at 1 year posttransplant, reflecting a greater level of confidence in its use after the early posttransplant period, when the risk of thrombosis and wound complications are diminished and the risk of nephrotoxicity increases (15).

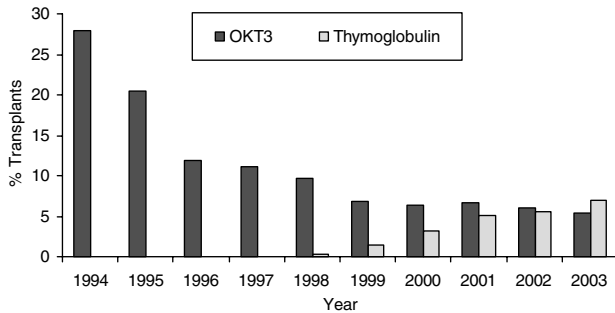
Minimization of immunosuppression (one-drug regimens) for liver transplantation

Monotherapy immunosuppression has grown from 4% of patients at the time of hospital discharge in 2000 to 12% in 2004, the vast majority (>80%) being on tacrolimus alone (SRTR analysis, May 2005). However, most practices attempting to achieve monotherapy immunosuppression, usually with a calcineurin inhibitor, select patients with stable graft function and frequently wean them from adjunctive immunosuppressants 6–12 months following transplantation. The OPTN/SRTR data reveal that at 1 year following transplantation, the proportion of recipients on monotherapy has increased to 34%, with 87% of these patients on tacrolimus alone, 6% on cyclosporine, 4% on sirolimus and <1% on mycophenolate mofetil. By 2 years, monotherapy is used for 46% of recipients, with 86% on tacrolimus alone, 7% on cyclosporine, 6% on sirolimus and 1% on mycophenolate mofetil. By 3 years following transplantation, 50% of liver recipients have achieved monotherapy status, with 85% on tacrolimus, 8% on cyclosporine, 5% on sirolimus and <1% on mycophenolate mofetil.

Antirejection treatment for liver transplantation

The incidence of acute rejection continues to decline from already low levels—in 2003, 18% of liver transplant recipients were reported to have experienced a rejection episode, a decrease from 24% the prior year. As noted previously, this decrease likely reflects both improved potency of immunosuppressive regimens and improved ability to distinguish between recurrent HCV and acute rejection (16).

Treatment of rejection continues to be primarily corticosteroid-based, with the vast majority of rejections being reversed with a short course or bolus of corticosteroids. Ninety-two percent of rejections were reversed by this approach or augmented baseline immunosuppression, while 18% were considered steroid-resistant and required antibody therapy. Within this group of antibody treatment of rejection, 5% of patients received an anti-CD3 monoclonal antibody, 7% an antithymocyte/lymphocyte globulin, 2% alemtuzumab and 4% an anti-IL-2 receptor antibody. Compared to previous years, this predominant use of the polyclonal antibodies is new (Figure 18).



Source: 2005 OPTN/SRTR Annual Report, Table 9.6i.

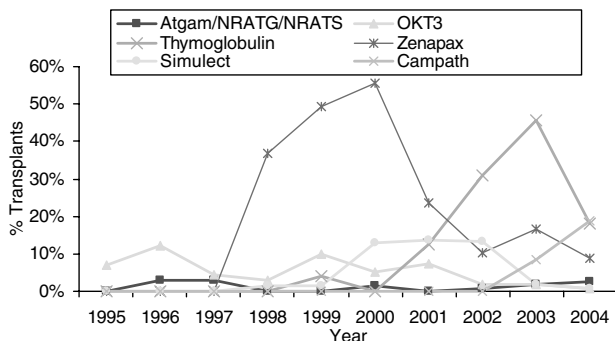
Figure 18: Percentage of OKT3 and thymoglobulin used in antirejection treatments, for liver transplants by year, 1994–2003.

Intestine Transplantation

The number of intestine transplants performed in the United States continues to increase but is still relatively small compared with other organs. In 1995, only 43 cases with data on immunosuppression were registered with the SRTR; this number increased to 148 in 2004. The interpretation of any trends in immunosuppression use is limited by the small total number of cases.

Induction immunosuppression for intestine transplantation

The use of induction therapy in intestine transplantation decreased to 50% in 2004, compared to 74% in 2003 and 57% in 2002. Alemtuzumab, rabbit antithymocyte globulin and daclizumab accounted for 92% of induction therapy (Figure 19). The use of alemtuzumab increased from 9% in 2003 to 19% in 2004, becoming the most commonly used induction agent in intestine transplantation. Over the year, alemtuzumab's use for induction replaced much of the use of rabbit antithymocyte globulin (down to 18% from 46%) and daclizumab (down to 9% from 16%).



Source: 2005 OPTN/SRTR Annual Report, Table 10.6a.

Figure 19: Trends in induction immunosuppression for intestine transplantation, 1995–2004.

Maintenance immunosuppression before discharge for intestine transplantation

Over the last decade, the overwhelming majority of intestine recipients have been maintained on tacrolimus, whose usage reached 98% in 2004. A very small percentage of intestine recipients received cyclosporine; 6% in 1995, 2% in 1997 and 8% in 1998. Although both azathioprine and mycophenolate mofetil were used between 1995 and 2001, the latter was the only antimetabolite used since, and it was prescribed for only 9% of patients in 2003 and 2004. Sirolimus was used for 12% of maintenance immunosuppression in 2004. From 2000 to 2004, tacrolimus/sirolimus was the most commonly used discharge regimen for intestine transplantation (15%), not the case for most other types of transplantation. The second most common discharge regimen during this period was tacrolimus/mycophenolate mofetil, which was administered to 8% of patients. As was the case for other solid organs, there has been an increasing trend toward implementing steroid-avoidance protocols; in 2004, 27% of patients were not administered steroids, compared to 7% and 4% in 1995 and 2000, respectively (SRTR analysis, May 2005).

Maintenance immunosuppression 1 and 2 years following intestine transplantation

In 2003, only 87 intestine recipients (75%) had immunosuppression information reported at the end of the first year following transplantation. Almost all intestine recipients are maintained on tacrolimus. The use of cyclosporine has diminished, reaching 1% in 2002 and 0% since. Antimetabolites were used for 9% of patients with mycophenolate mofetil, the only prescribed antimetabolite in 2003 (9%). As was the case at discharge, sirolimus was the only TOR inhibitor used (16% in 2003). Tacrolimus alone or with steroids has been the most commonly used regimen 1 year and 1 years following intestine transplantation. In general, a very low percentage of intestine recipients continued using the discharge regimens tacrolimus/rapamycin or tacrolimus/mycophenolate mofetil by 2 years after transplantation. There has been a general trend toward increasing steroid-withdrawal rate at 1 year among first intestine recipients, reaching a maximum of 29% in 2003 (SRTR analysis, May 2005).

Antirejection treatment for intestine transplantation

Over the last decade, there has been an overall decrease in the incidence of graft rejection requiring treatment during the first year following intestine transplantation. In 1997, the incidence of graft rejection was 68%, which decreased to 37% in 2001, 45% in 2002 and 56% in 2003. This decline is associated with the use of modified induction therapy agents, particularly daclizumab, which was not used before 1998 (Figure 20). In 2003, corticosteroids were the most commonly used agent to treat rejection (92%), followed by antibodies (39%). Muromonab-CD3 continued to be the

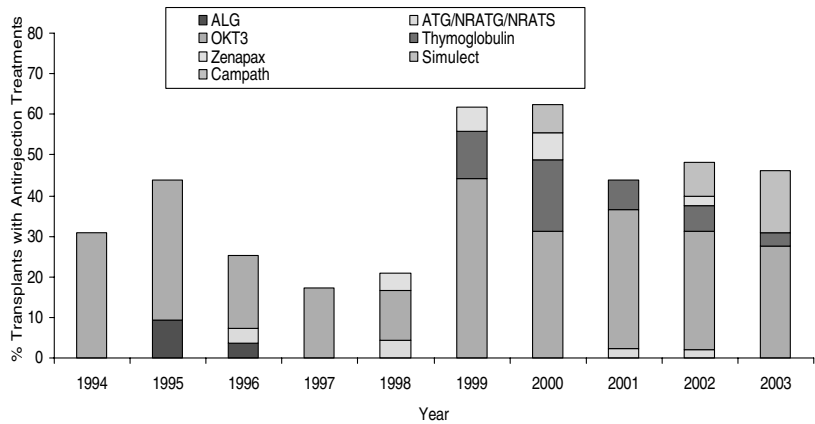


Figure 20: Trends in antibody therapy for rejection episodes in first year following intestine transplantation, 1994–2003.

Source: 2005 OPTN/SRTR Annual Report, Table 10.6i.

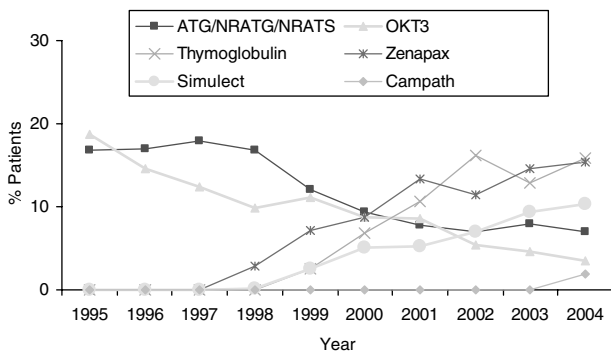
most commonly administered antibody therapy in intestine transplantation (28%), followed by alemtuzumab (15%, up from 8% in 2002) and rabbit antithymocyte globulin (3%).

Heart Transplantation

Induction immunosuppression for heart transplantation

The use of an induction regimen in heart transplant recipients, and the various types of agents utilized, has gradually changed over the last decade. While the frequency of the administration of these agents remains far below that seen currently in kidney transplantation, and below the rates seen in heart transplantation during the late 1980s and early 1990s, there has been a gradual increase in their use in the past 6 years. Figure 21 shows the changing patterns for induction therapy from 1995 through 2004.

During the past decade, there was a decline in the percentage of recipients receiving an induction agent to a low of 30% in 1998, but this has risen to a high of 47% in 2003



Source: 2005 OPTN/SRTR Annual Report, Table 11.6a.

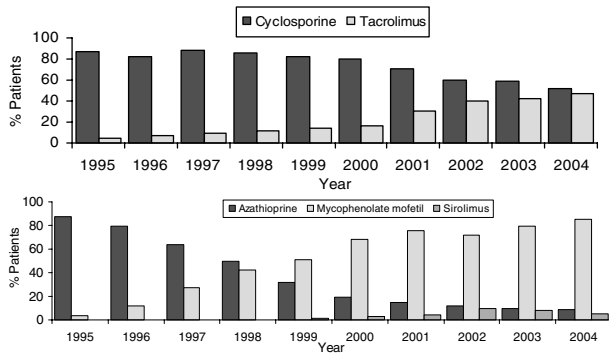
Figure 21: Trends in induction immunosuppression for heart transplantation, 1995–2004.

and 2004. Center-specific practice patterns, combined with recipient comorbidities (renal dysfunction or a high risk for rejection), have often been cited as the primary influences on the use and choice of specific agents. Muromonab-CD3 and antithymocyte globulin (equine) were the most commonly used perioperative induction agents until 2000. Seventeen percent of patients received antithymocyte globulin (equine) in 1995, compared to only 7% in 2004. Similarly, 19% received muromonab-CD3 in 1995 versus only 4% in 2004. Practice patterns have changed with the clinical availability of new agents, and with concerns regarding perceived increased risks of vascular rejection (secondary to human anti-murine antibody development), cytomegalovirus infection, and lymphoproliferative disease. The use of antithymocyte globulin (rabbit) in heart transplantation increased from 0% in 1998 to 16% in 2004. Similarly, the use of the anti-IL-2 receptor antibodies, daclizumab and basiliximab, increased from 0% in 1997 to 26% (15.4% for daclizumab, 10.3% for basiliximab) in 2004. Alemtuzumab was used for 2% of heart recipients in 2004, the first year its use has been reported.

In the cohort of patients transplanted between 2000 and 2004, the three most commonly used maintenance regimens at the time of discharge were cyclosporine/mycophenolate mofetil (47% of patients receiving induction), tacrolimus/mycophenolate mofetil (24%) and cyclosporine/azathioprine (9%).

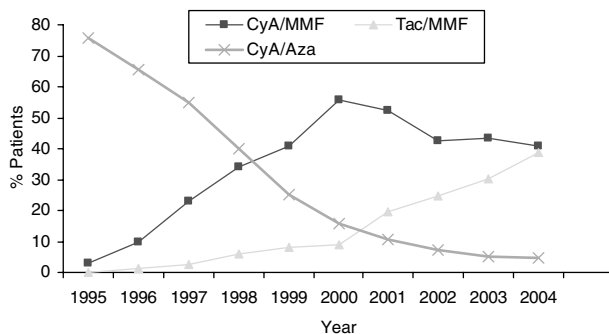
Maintenance immunosuppression before discharge for heart transplantation

Figure 22 shows the trends over the past 10 years in maintenance immunosuppressive therapy prior to discharge. Cyclosporine-based regimens have decreased steadily from 87% in 1995 to 51% in 2004 (66% of which is with Neoral and 28% is with Gengraf). Conversely, the use of tacrolimus-based regimens has increased from 4% in 1995 to 47% in 2004. Since the introduction of generic formulations of cyclosporine in 2000, their administration has



Source: 2005 OPTN/SRTR Annual Report, Table 11.6e.

Figure 22: Trends in maintenance immunosuppression prior to discharge for heart transplantation, 1995–2004.

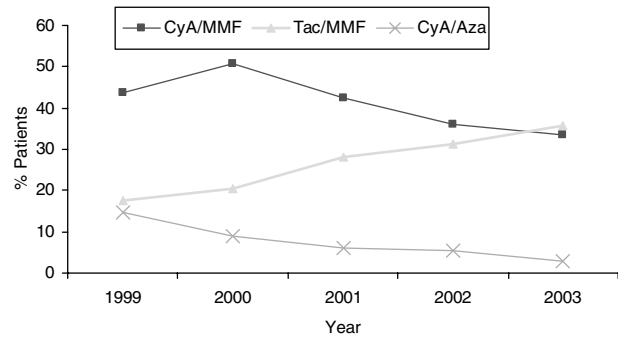


Source: 2005 OPTN/SRTR Annual Report, Table 11.6d.

Figure 23: Trends in discharge immunosuppression regimens for heart transplantation, 1995–2004.

steadily increased from 2% of the total cyclosporine use to 29% in 2004. Prescription of azathioprine has had a steady decrease from 87% in 1995 to 9% in 2004, while utilization of mycophenolate mofetil has increased, rising from 3% in 1995 to 85% in 2004. Sirolimus usage prior to discharge peaked at 10% in 2002 and dropped to 5% in 2004. While corticosteroids are still used for the majority of patients, there has been a slight downward trend from a high of 97% in 2001 to 92% in 2004.

At the time of discharge, the most common regimens are cyclosporine/mycophenolate mofetil in 41% and tacrolimus/mycophenolate mofetil in 39%, the latter being the fastest-growing regimen over the past decade (Figure 23). Both of these regimens are used with concomitant steroids 95% of the time. The use of a tacrolimus/sirolimus regimen peaked at 6% in 2002, at the time of an ongoing multi-center clinical trial, and has declined to only 1% of the patients in 2004. Cyclosporine/azathioprine, which was by far the most common regimen through the 1980s and mid-1990s, is now rarely used (4.6% in 2004). Interestingly, 2.1% of patients



Source: 2005 OPTN/SRTR Annual Report, Table 11.6f.

Figure 24: Trends in immunosuppression maintenance regimens, 1 year posttransplant for heart transplantation, 1999–2003.

were not on any calcineurin inhibitor at the time of discharge, being maintained only on sirolimus/mycophenolate mofetil—and, presumably, steroids.

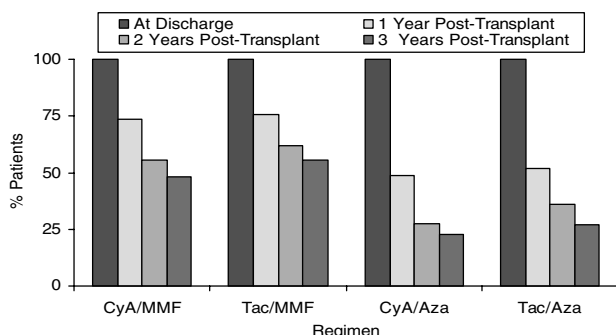
Maintenance immunosuppression 1 and 2 years following heart transplantation

In the most recent cohort (2003), by 1 year after transplantation, use of tacrolimus-based regimens increased to 50% while that of cyclosporine-based regimens decreased to 43% (Figure 24). Of these tacrolimus-based regimens, tacrolimus/mycophenolate mofetil remains the most commonly prescribed, at 36%. This represents the first time that tacrolimus-based regimens were employed more frequently than the regimens based on cyclosporine. Sirolimus as part of the regimen was used for 11% of patients at 1 year following transplantation in the 2003 cohort.

At 2 years following transplantation the most common maintenance regimens are mycophenolate mofetil combined with cyclosporine or tacrolimus (36% and 31%, respectively). Tacrolimus combined with rapamycin is the third most common regimen, used for 6% of the patients. A calcineurin inhibitor-free regimen using sirolimus/mycophenolate mofetil was used at 2-year follow-up for 0.1% of the patients transplanted in 2002.

Maintenance regimen change and discontinuation for heart transplantation

An interesting analysis performed for this report looked at the percentage of patients on the same regimen at discharge over 3 years following transplantation, for a cohort of patients who received transplants from 1999 to 2003. Not surprisingly, the greatest change occurs during the first year, presumably in response to the occurrence of rejection, infection and drug side effects. Ongoing ‘regimen attrition’ occurs during subsequent years. Figure 25 shows the changes over time for the four regimens most commonly used at discharge.



Source: 2005 OPTN/SRTR Annual Report, Table 11.6h.

Figure 25: Percentage of heart transplant patients still on discharge regimens at 1, 2 and 3 years posttransplant, for the four most common regimens in 2001.

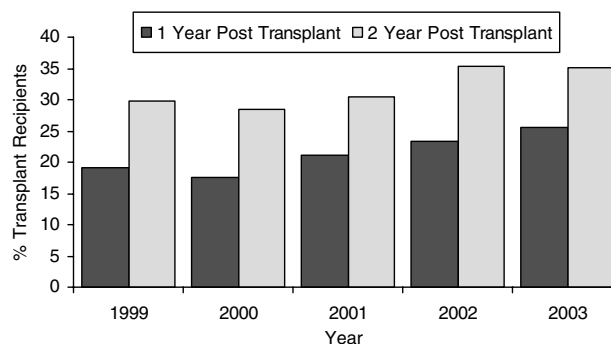
For the most commonly used regimens, the highest rate of conservation of the original discharge prescription was seen in the tacrolimus/mycophenolate mofetil group with 49–56% of patients still receiving it 3 years after transplantation. For the cyclosporine/mycophenolate mofetil group, 47–51% were still receiving it 3 years after transplantation. The highest rate of regimen change occurred in the cyclosporine/azathioprine group, of which only 21% were still receiving it at 3 years.

Steroid withdrawal and steroid avoidance for heart transplantation

In the 2004 year cohort, a total of 139 patients had avoided corticosteroids at discharge, representing 8% of those receiving heart transplants. Despite the small numbers involved, this represents a relatively large (nearly threefold) increase in this practice, a rise from only 3% of patients in 2001. Of this steroid avoidance group, the most common maintenance regimens were tacrolimus/mycophenolate mofetil and cyclosporine/mycophenolate mofetil (38% and 42% of those undergoing steroid avoidance, respectively).

An analysis of steroid avoidance based on the use of induction therapy in all patients in the 2000–2004 cohort showed that 5% of the patients had avoided steroids at the time of discharge. Of this group, 44% had not received any induction therapy. Of the 56% that had received induction therapy, the most commonly used induction agent was antithymocyte globulin (rabbit), representing 46% of those receiving induction and 26% of the entire steroid-avoidance group.

Analyses, presented in Figure 26, evaluated the steroid-withdrawal rates at 1 and 2 years following transplantation, based on the original maintenance regimen at the time of discharge. In 2003, 26% of those patients receiving steroids at the time of discharge were completely removed from steroids 1 year later—the highest rate in the past 5 years. The most common discharge



Source: 2005 OPTN/SRTR Annual Report, Table 15.6.2 and 15.6.3.

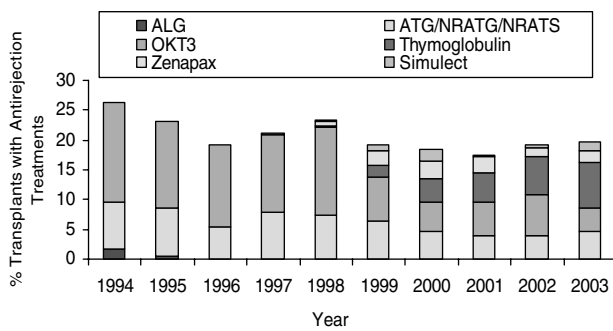
Figure 26: Steroid-withdrawal rates at 1 and 2 years post-transplant for heart transplants, 1999–2003.

maintenance regimen associated with steroid withdrawal was cyclosporine/mycophenolate mofetil, used for 46% of the total steroid-withdrawal group; 23% of the entire cyclosporine/mycophenolate mofetil group was removed from steroids by 1 year. The second most common discharge maintenance regimen associated with steroid withdrawal was tacrolimus/mycophenolate mofetil, used for 30% of the total steroid-withdrawal group; 27% of the entire tacrolimus/mycophenolate mofetil group was steroid-free at 1 year following transplantation.

Similar trends were seen when evaluating steroid-withdrawal rates at 2 years following transplantation. For the cohort of patients who received heart transplants in 2002, 35% had steroids withdrawn by 2 years (up from 26% at 1 year). The cyclosporine/mycophenolate mofetil group made up 45% of the entire steroid-withdrawal group; 34% of this subgroup underwent steroid withdrawal. The tacrolimus/mycophenolate mofetil group made up 23% of the entire steroid withdrawal group, with a 34% rate of steroid withdrawal within the tacrolimus/mycophenolate mofetil group.

Antirejection treatment for heart transplantation

Despite fluctuations over the past decade, there has been an overall trend toward less use of all types of antirejection therapy. In 2003, 654 patients of a total cohort of 2057 received antirejection therapy (32%, down from a 10-year high of 42% in 1998). The incidence of rejection in the first year after transplant over the past 10 years has decreased. This trend may reflect a true decrease in acute rejection rates associated with the more modern maintenance regimens. Another factor contributing to this decline may be that more rejection episodes are being treated with only a change in maintenance agents, resulting in the possibility that decreased rates of rejection may represent an under-reporting of rejection episodes as measured by the use of antirejection therapy.



Source: 2005 OPTN/SRTR Annual Report, Table 11.6i.

Figure 27: Trends in antibody therapy for rejection episodes in first year following heart transplantation, 1994-2003.

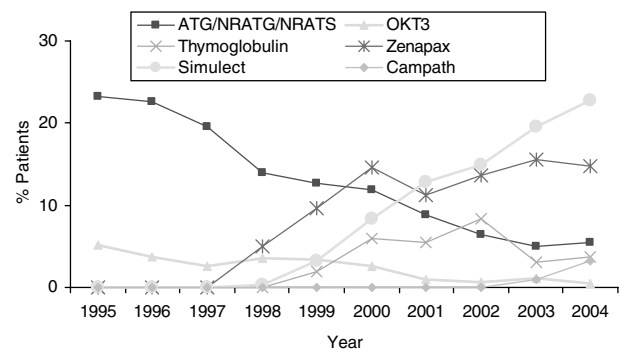
The great majority of patients (92%) with reported antirejection therapy received corticosteroids. Eighteen percent received an antilymphocyte antibody preparation, the most common being antithymocyte globulin (rabbit) for 40% of that group, followed by antithymocyte globulin (equine) for 25% and muromonab-CD3 for 22%. Of interest, 18% of the antibody-treated group received an anti-IL-2 receptor antibody, despite a lack of data supporting the use of this class for the treatment of rejection. Figure 27 shows the distribution over the past 10 years of antilymphocyte antibody use for antirejection treatment in the first year after transplant.

Lung Transplantation

Induction immunosuppression for lung transplantation

The use and types of an induction regimen for lung transplant recipients evolved over the last decade. Figure 28 shows the changing patterns for induction therapy from 1995 through 2004. The use of induction therapy has increased from 22% in 1997 to 50% in 2004, the highest rate in 10 years. Administration of antithymocyte globulin (equine), the most commonly used perioperative induction agent from 1995 to 1999, steadily decreased from 23% in 1995 to 5% in 2004. The most rapid growth has been seen with the anti-IL-2 receptor antibody class, increasing from 0% in 1997 to 38% in 2004 (23% for basiliximab, 15% for daclizumab). Basiliximab is currently the most commonly used induction agent in lung transplantation, accounting for 46% of all induction therapy used. The use of antithymocyte globulin (rabbit) decreased from a high of 8% in 2002 to 4% in 2004, and muromonab-CD3 is essentially no longer used (0.5% in 2004). Alemtuzumab was first reported in 2003 for 0.9% of recipients and its prescription increased to 3% in 2004.

Among the cohort of patients transplanted between 2000 and 2004, for the four most commonly used maintenance regimens at the time of discharge, an in-



Source: 2005 OPTN/SRTR Annual Report, Table 12.6a.

Figure 28: Trends in induction immunosuppression for lung transplantation, 1995-2004.

duction regimen was utilized for 38% of patients on cyclosporine/mycophenolate mofetil, 52% of patients on tacrolimus/mycophenolate mofetil, 52% of patients on tacrolimus/azathioprine and 40% of patients on cyclosporine/azathioprine.

Maintenance immunosuppression before discharge for lung transplantation

The use of cyclosporine-based regimens for maintenance therapy before discharge has decreased steadily from 77% in 1995 to 30% in 2004; 69% of cyclosporine therapy is with Neoral. Conversely, prescription of tacrolimus-based regimens increased over the same period, from 9% in 1995 to 70% in 2004 (Figure 29). Similarly, azathioprine therapy has had a steady decline from 88% in 1995 to 44% in 2004, while mycophenolate mofetil administration increased from 3% in 1995 to 46% in 2004. Sirolimus use before discharge peaked at 4% in 2001, but it decreased to only 1% in 2004, in response to safety issues associated with impairment of bronchial anastomotic healing. Corticosteroids are still used for the majority of patients (97% in 2004), as they have been for the last 10 years.

At the time of discharge, the most common regimens are tacrolimus/mycophenolate mofetil (the fastest growing regimen over the past decade), used for 36% of recipients; tacrolimus/azathioprine (25.1%); cyclosporine/azathioprine (16.4%), which was the most common regimen through the 1980s and mid-1990s); and cyclosporine/mycophenolate mofetil (10.1%). Calcineurin inhibitor-free regimens are essentially not used at the time of discharge.

Maintenance immunosuppression 1 and 2 years following lung transplantation

In the most recent cohort (those who received transplants in 2003), by 1 year following transplantation the use of tacrolimus-based regimens increased to 71% while the use of cyclosporine-based regimens

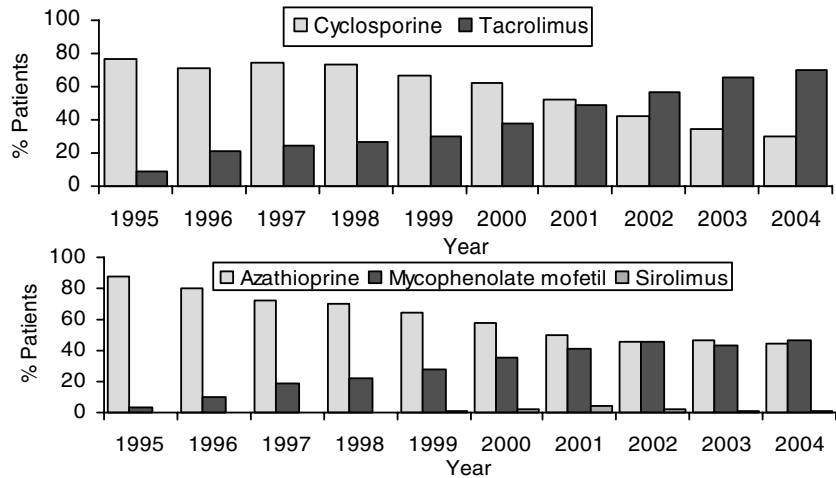
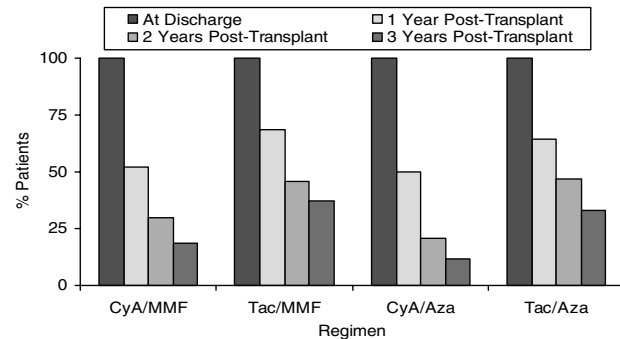


Figure 29: Trends in maintenance immunosuppression prior to discharge for lung transplantation, 1995–2004.

Source: 2005 OPTN/SRTR Annual Report, Table 12.6e.

decreased to 21%. Of these tacrolimus-based regimens, tacrolimus/mycophenolate mofetil remains the most commonly employed (35%), followed by tacrolimus/azathioprine (23%). Sirolimus was used as part of a regimen for only 5% of patients at 1 year following transplantation.

At 2 years following transplantation (for those who received transplants in 2002), the most common maintenance regimens are tacrolimus combined with mycophenolate mofetil (33%) or azathioprine (22%). Cyclosporine is only administered in 21% of the regimens.



Source: 2005 OPTN/SRTR Annual Report, Table 12.6h.

Figure 30: Percentage of lung transplant patients still on original discharge regimens at 1, 2 and 3 years posttransplant, for the four most common regimens in 2001.

Maintenance regimen change and discontinuation for lung transplantation

An interesting analysis performed for this report examined the percentage of patients remaining on the same regimen at discharge over 3 years following transplant. The greatest changes occurred during the first year, presumably in response to the occurrence of rejection, infection and drug side effects. However, regimens continued to be modified after the first year, reflecting persistent long-term problems following lung transplantation, including the high incidence of late infections and chronic rejection. Figure 30 shows the changes over time for the four regimens most frequently administered at discharge.

For the most commonly used regimens, the rate of conservation of the original discharge regimen in the 2002 tacrolimus/mycophenolate mofetil group was only 54% at 3 years following transplantation (yet it was the highest for all the regimens). For the 2001 tacrolimus/azathioprine group it was only 33%, and for the 2002 cyclosporine/mycophenolate mofetil group it was only 16%. The highest rate of regimen change occurred in the cyclosporine/azathioprine group, of which only 12% were still on the original regimen at 3 years.

Steroid withdrawal and steroid avoidance for lung transplantation

In the 2004 cohort, only 31 patients had avoided corticosteroids at discharge, representing 3% of all those receiving lung transplants. This represents a stable steroid-avoidance rate over the past 10 years (SRTR analysis, May 2005).

When analyzing the rate of steroid avoidance based on the use of induction therapy in all patients who received lung transplants between 2000 and 2004 cohort, 3% of the patients had avoided steroids at the time of discharge, 54% of whom had not received any induction therapy. Among those that did receive induction therapy, the most commonly used induction agent was an anti-IL-2 receptor antibody agent, representing 67% of those receiving induction and 31% of the entire steroid-avoidance group.

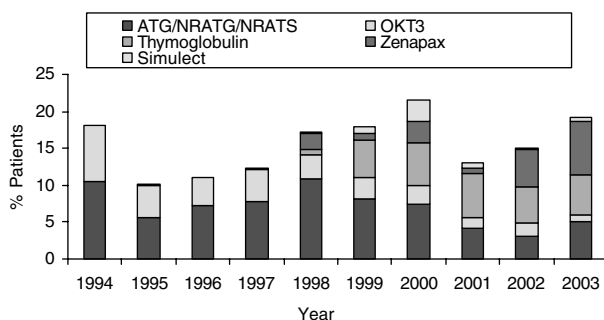
An analysis of the steroid-withdrawal rate at 1 year following transplantation, based on the original maintenance

regimen at the time of discharge demonstrated that in 2003, only 2% of those patients on steroids at the time of discharge were completely off them 1 year later, representing the lowest rate among any solid-organ transplants. There has been no change in this rate over the past 5 years. Furthermore, a backward trend was seen when evaluating steroid-withdrawal rates at 2 years posttransplant. Only 2% of the 2002 patient cohort had steroids withdrawn by 2 years—down from 4% at 1 year in the same 2002 group, indicating a small net increase in the rate of steroid use (SRTR analysis, May 2005).

Antirejection treatment for lung transplantation

Over the past decade there has been a small trend toward less use of all types of antirejection therapy. In 2003, 354 patients of a total cohort of 1099 received antirejection therapy (32%, down from a 10-year high of 53% in 1995). The incidence of rejection in the first year after transplant over the past 10 years has dropped. While this drop may indeed result from a decrease in acute rejection rates associated with the more modern maintenance regimens, there are other possible explanations as well. First, it is possible that more rejection episodes are being treated with only a change in the maintenance agents, which could lead to underreporting of rejection episodes as measured by the use of antirejection therapy. Second, a change in practice patterns toward fewer surveillance biopsies in many lung transplant programs may yield a lower detection rate and thus a falsely low reported rejection rate.

The great majority of patients (96%) requiring antirejection therapy received corticosteroids. In the 2003 cohort, 16% received an antilymphocyte antibody preparation. Surprisingly, the most common agent used was daclizumab (43%), despite a lack of data supporting the use of this class of agents in treating rejection. Figure 31 shows the distribution of antilymphocyte antibody use for the treatment of rejection in the first year after transplant over the past 10 years.



Source: 2005 OPTN/SRTR Annual Report, Table 12.6i.

Figure 31: Trends in antibody therapy for rejection episodes in first year following lung transplantation, 1994–2003.

Heart-Lung Transplantation

With only 39 heart-lung transplants performed in 2004, it is difficult to make any definitive statements regarding changing patterns in immunosuppressive agent use. As a general observation, the changes in immunosuppression that have occurred in heart-lung transplantation seem to reflect changes that have occurred in isolated lung transplantation more than those seen in isolated heart transplantation. Since this type of transplant is performed at so few centers, it is likely that patterns in immunosuppressive agent use are more related to protocol changes at the small subgroup of those centers performing more than five transplants per year.

Induction immunosuppression for heart-lung transplantation

During the past decade, the use of induction therapy was at a low of 24% in 1998 and at a high of 73% in 2001, with a rate of 60% in 2004. Use of antithymocyte globulin (equine), the most commonly used perioperative induction agent from 1995 through 2000, decreased from 44% in 1995 to 14% in 2004. The most rapid growth has been seen with the anti-IL-2 receptor antibody class—increasing from 0% in 1998 to 30% in 2004 (19% for daclizumab, 11% for basiliximab). Daclizumab is currently the most commonly used induction agent in heart-lung transplantation, accounting for 32% of all induction therapy. The administration of antithymocyte globulin (rabbit) has also increased and represented 23% of antibody induction prescribed in 2004. Alemtuzumab was first reported in 2004; it was used for 5% of the patients.

In the cohort of patients transplanted between 2000 and 2004, for the four most commonly used maintenance regimens at the time of discharge, an induction regimen was used for 72% of patients on cyclosporine/mycophenolate mofetil, 52% of patients on tacrolimus/mycophenolate mofetil, 75% of patients on tacrolimus/azathioprine and 71% of patients on cyclosporine/azathioprine.

Maintenance immunosuppression before discharge for heart-lung transplantation

Over the past 10 years, use of cyclosporine-based regimens for maintenance therapy before discharge decreased from 76% in 1995 to 38% in 2004. Conversely, tacrolimus-based regimens steadily increased over the same period, from 14% in 1995 to 65% in 2004. Similarly, the use of azathioprine decreased from 95% in 1995 to 32% in 2004, while mycophenolate mofetil administration increased, rising from 0% in 1995 to 50% in 2004. Sirolimus use before discharge was at its highest in 2003 (6%), the first year it appeared; its use has decreased in response to safety issues associated with impairment of airway anastomotic healing, dropping to only 3% in 2004. Corticosteroids were used for 100% of the patients in 2004.

At the time of discharge, 32% of patients received tacrolimus/mycophenolate mofetil, the most common regimen and the only one whose use has increased over the past decade. Cyclosporine/azathioprine, the most common regimen from the 1980s through the mid-1990s, was employed for only 15% of patients in 2004. No use of calcineurin inhibitor-free regimens at the time of discharge has been reported.

Maintenance immunosuppression 1 and 2 years following heart-lung transplantation

In the most recent cohort (those who received a heart-lung transplant in 2003), by 1 year following transplantation, the use of tacrolimus-based regimens increased to 77% while cyclosporine-based regimens decreased to 23%. Of these tacrolimus-based regimens, tacrolimus/mycophenolate mofetil remains the most commonly used (36%), followed by tacrolimus/azathioprine (23%). At 2 years following transplantation, the various drug combination regimens are all represented.

Due to small numbers of patients for the 1999–2003 cohort in each immunosuppressive combination, it is not possible to comment on trends in regimen changes 3 years after transplantation.

Steroid withdrawal and steroid avoidance for heart-lung transplantation

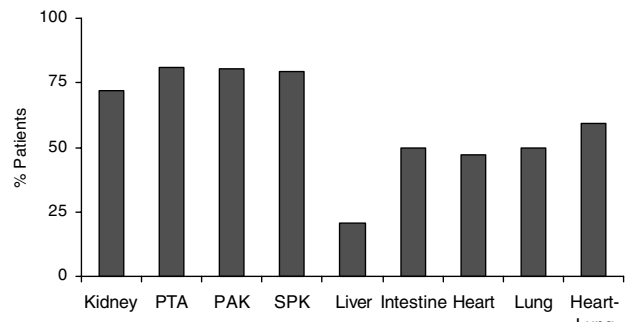
Neither steroid avoidance nor steroid withdrawal has been performed in the most recent cohorts of heart-lung transplants (SRTR analysis, May 2005).

Antirejection treatment for heart-lung transplantation

Data are available on only eight heart-lung transplant recipients with reported rejection in 2003. Sixty-two percent received corticosteroids and 12% received antithymocyte globulin (equine).

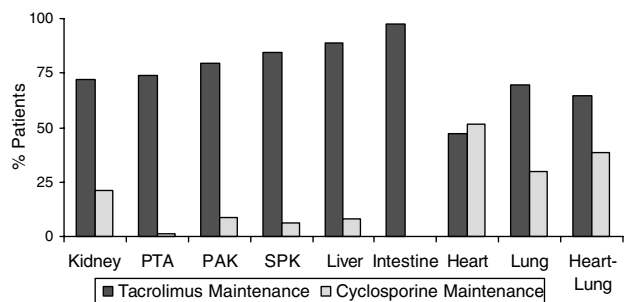
Comparisons Between Organs

Over the past decade, the use of induction therapy in solid-organ transplantation has increased for all organs except for combined heart-lung transplants. Increases have ranged from modest to dramatic. In 2003 and 2004, induction immunosuppression was most commonly employed for pancreas (PTA 81%, SPK 80% and PAK 80%) and kidney (72%) transplant recipients, and least commonly for liver transplant recipients (20%). In addition, induction strategies were used for roughly half of all heart-lung (60%), lung (50%), intestine (50%) and heart (47%) recipients (Figure 32). Polyclonal antibody induction with antithymocyte globulin of equine or antithymocyte globulin of rabbit is the most frequent choice for kidney and pancreas transplantation. Anti-IL-2 receptor antibody induction with basiliximab or daclizumab is more common for liver, heart-lung, lung and heart transplantation. Alemtuzumab is coming into more frequent usage, accounting for 43%



PTA: Pancreas Transplant Alone. PAK: Pancreas After Kidney. SPK: Simultaneous Pancreas-Kidney. Source: 2005 OPTN/SRTR Annual Report, Table 1.9.

Figure 32: Comparative use of induction immunosuppression prior to discharge, by organ, 2004.



PTA: Pancreas Transplant Alone. PAK: Pancreas After Kidney. SPK: Simultaneous Pancreas-Kidney. Source: 2005 OPTN/SRTR Annual Report, Table 1.9.

Figure 33: Comparative calcineurin inhibitor use for immunosuppression prior to discharge, by organ, 2004.

of PTA, 19% of SPK and PAK and 19% of intestine transplant induction. It is now the most common agent used for induction in intestine transplantation.

With the exception of those who received a solitary pancreas transplant (PTA 76% and PAK 88%), calcineurin inhibitors are prescribed for 90% or more for all categories of solid-organ recipients at discharge from the initial transplant hospitalization (Figure 33). Except in the instance of heart transplantation (47%), 65% or more of all solid-organ transplant recipients receive tacrolimus. The changes in calcineurin inhibitor since 1995 are summarized in Table 2. At discharge, antimetabolite usage varies from a low of 9% for intestine recipients to a high of 95% for heart recipients. The use of mycophenolate mofetil predominates, with fewer than 3% of recipients receiving azathioprine in all abdominal organ transplantation. In contrast, azathioprine is prescribed for 9% of heart, 44% of lung, and 32% of heart-lung recipients. Sirolimus use is uncommon (<6%) in lung, heart-lung, heart and liver transplantation, but has gained more acceptance for SPK (17%), PAK (16%), PTA (12%), kidney (12%) and intestine (12%) recipients.

Table 2: Calcineurin inhibitor use for immunosuppression before discharge, by organ, 1995 vs. 2004

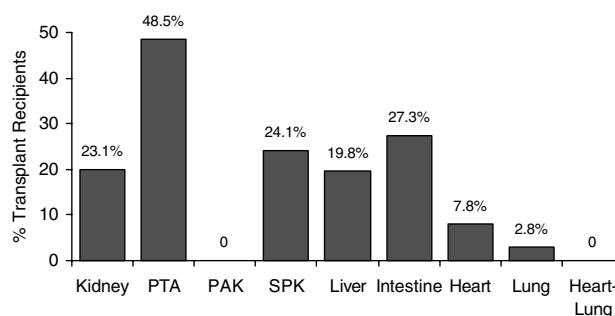
Organ	Tacrolimus		Cyclosporine	
	1995	2004	1995	2004
Kidney	6.7%	72.1%	81.7%	21.1%
PTA	58.3%	74.2%	36.1%	1.3%
PAK	53.3%	79.6%	36.7%	8.6%
SPK	36.6%	84.3%	58.2%	6.4%
Liver	47.5%	88.8%	47.1%	8.0%
Intestine	93.5%	97.6%	6.5%	0.0%
Heart	4.3%	47.1%	86.7%	51.3%
Lung	9.1%	69.8%	77.0%	29.7%
Heart-lung	13.6%	64.7%	76.3%	38.2%

PTA, pancreas transplant alone; PAK, pancreas after kidney; SPK, simultaneous pancreas-kidney.
 Source: 2005 OPTN/SRTR Annual Report, Tables 5.6e, 6.6e, 7.6e, 8.6e, 9.6e, 10.6e, 11.6e, 12.6e and 13.6e.

At the end of the first year following transplantation, 83% or more of all solid-organ recipients receive a calcineurin inhibitor. Tacrolimus is the predominant calcineurin inhibitor employed for maintenance immunosuppression of all categories of solid organs. Except in the cases of PTA (53%), liver (37%) and intestine (7%), 75% or more of solid-organ maintenance immunosuppression regimens include an antimetabolite. Again, only among recipients of thoracic organs is azathioprine use seen for more than 2% of patients. The use of sirolimus generally increases during the first year. By the end of the first year, it is employed for 23% of SPK, 23% of PAK, 21% of PTA, 18% of kidney, 15% of heart, 10% of liver, 9% of lung and 8% of intestine recipients. During the first posttransplant year, the use of sirolimus increases for all but heart-lung and intestine transplant recipients.

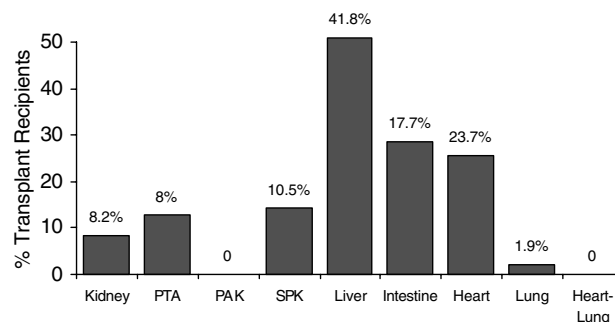
Steroid avoidance is an emerging trend in solid-organ transplantation. In 2004, 48% of PTA, 28% of living donor kidney, 27% of intestine, 24% of SPK, 22% of living donor liver, 20% of deceased donor kidney, 20% of deceased donor liver, 8% of heart, 4% of living donor lung and 3% of deceased donor lung transplant recipients were not prescribed corticosteroids at discharge from their initial transplant hospitalization, as seen in Figure 34 (SRTR analysis, May 2005). By the end of the second posttransplant year, the steroid-withdrawal rate decreased for all but deceased donor liver (66%), living donor liver (63%), heart (35%) and living donor lung (8%).

Despite the growing application of steroid avoidance and withdrawal as seen in Figures 34 and 35, 'triple immunosuppression' with a calcineurin inhibitor, corticosteroid and either an antimetabolite or a TOR inhibitor predominates at discharge and at 2 years following transplantation for those transplanted between 1995 and 2004, and between 1998 and 2002, respectively. Except for the discipline of intestine transplantation, where immunosuppression with



Source: 2005 OPTN/SRTR Annual Report, Tables 15.4a, 15.5a, 15.6, and SRTR analysis.

Figure 34: Steroid avoidance rates for all deceased donor transplants, 2004.



Source: 2005 OPTN/SRTR Annual Report, Tables 15.4a, 15.5a, 15.6, and SRTR analysis.

Figure 35: Steroid-withdrawal rates at 1 year posttransplant for all deceased donor transplants, 2003.

tacrolimus monotherapy (23% at discharge and 22% at 2 years), tacrolimus plus corticosteroids (56% at discharge and 42% at 2 years) and tacrolimus plus sirolimus and corticosteroids (7% at discharge and 20% at 2 years) are common, the most frequently employed immunosuppressive regimen is the combination of tacrolimus, mycophenolate mofetil and corticosteroids. Only in the case of heart transplantation does the prescription of the combination of cyclosporine, mycophenolate mofetil and corticosteroids (39% at discharge and 28% at 2 years), exceed that of tacrolimus, mycophenolate mofetil and corticosteroids (36% at discharge and 24% at 2 years).

Among those transplanted in 2003 and treated for rejection during the first posttransplant year, corticosteroids were administered to 62–96% of recipients (heart-lung and lung, respectively). Antibody use varied from 12% (heart-lung) to 77% (PTA). The administration of alemtuzumab as therapy for rejection is rising especially in intestine (15%), PAK (28%) and PTA (42%) transplantation.

As the number of available choices expands, the mosaic of the practice of immunosuppression in transplantation becomes more textured. New protocols emerge and displace previous behaviors. This article reviews and describes a number of these trends, including the increased application of corticosteroid avoidance and withdrawal, the evolution toward tacrolimus-centered immunosuppression, and the emerging use of alemtuzumab.

Acknowledgments

The Scientific Registry of Transplant Recipients is funded by contract number 231–00–0116 from the Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services. The views expressed herein are those of the authors and not necessarily those of the U.S. Government. This is a U.S. Government-sponsored work. There are no restrictions on its use.

The authors thank Jeong Park, Pharm.D., for her assistance.

This study was approved by HRSA's SRTR project officer. HRSA has determined that this study satisfies the criteria for the IRB exemption described in the "Public Benefit and Service Program" provisions of 45 CFR 46.101(b)(5) and HRSA Circular 03.

References

1. Levine GN, McCullough KP, Rodgers AM, Dickinson DM, Ashby VB, Schaubel DE. Analytical methods and database design: Implications for transplant researchers, 2005. *Am J Transplant* 2006; 6(Part 2): 1228–1242.
2. Gruessner RWG. Immunobiology, diagnosis, and treatment of pancreas graft rejection. In: Gruessner RWG, Sutherland DE, eds. *Transplantation of the Pancreas*. New York: Springer-Verlag, 2004: 349–380.
3. Gruessner AC, Sutherland DE. Pancreas transplant outcomes for United States (US) and non-US cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of June 2004. *Clin Transplant* 2005; 19: 433–455.
4. Gruessner RW, Kandaswamy R, Humar A, Gruessner AC, Sutherland DE. Calcineurin inhibitor- and steroid-free immunosuppression in pancreas-kidney and solitary pancreas transplantation. *Transplantation* 2005; 79: 1184–1189.
5. Eason JD, Nair S, Cohen AJ, Blazek JL, Loss GE, Jr. Steroid-free liver transplantation using rabbit antithymocyte globulin and early tacrolimus monotherapy. *Transplantation* 2003; 75: 1396–1399.
6. Raimondo ML, Burroughs AK. Single-agent immunosuppression after liver transplantation: What is possible? *Drugs* 2002; 62: 1587–1597.
7. Marcos A, Eghtesad B, Fung JJ et al. Use of alemtuzumab and tacrolimus monotherapy for cadaveric liver transplantation: With particular reference to hepatitis C virus. *Transplantation* 2004; 78: 966–971.
8. Bucuvalas JC, Zeng L, Anand R. Predictors of length of stay for pediatric liver transplant recipients. *Liver Transpl* 2004; 10: 1011–1017.
9. Wiesner RH, Shorr JS, Steffen BJ, Chu AH, Gordon RD, Lake JR. Mycophenolate mofetil combination therapy improves long-term outcomes after liver transplantation in patients with and without hepatitis C. *Liver Transpl* 2005; 11: 750–759.
10. Neyts J, Meerbach A, McKenna P, De Clercq E. Use of the yellow fever virus vaccine strain 17D for the study of strategies for the treatment of yellow fever virus infections. *Antiviral Res* 1996; 30: 125–132.
11. Firpi RJ, Nelson DR, Davis GL. Lack of antiviral effect of a short course of mycophenolate mofetil in patients with chronic hepatitis C virus infection. *Liver Transpl* 2003; 9: 57–61.
12. Fasola CG, Heffron TG, Sher L et al. Multicenter randomized hepatitis C (HCV) three trial post liver transplantation (OLT): A one-year follow up report (abstract). *Am J Transplant* 2005; 5(Suppl 11): 276.
13. Jain A, Kashyap R, Dodson F et al. A prospective randomized trial of tacrolimus and prednisone versus tacrolimus, prednisone and mycophenolate mofetil in primary adult liver transplantation: A single center report. *Transplantation* 2001; 72: 1091–1097.
14. Mele TS, Halloran PF. The use of mycophenolate mofetil in transplant recipients. *Immunopharmacology* 2000; 47: 215–245.
15. Nair S, Eason J, Loss G. Sirolimus monotherapy in nephrotoxicity due to calcineurin inhibitors in liver transplant recipients. *Liver Transpl* 2003; 9: 126–129.
16. Shapiro R, Young JB, Milford EL, Trotter JF, Bustami RT, Leichtman AB. Immunosuppression: Evolution in practice and trends, 1993–2003. *Am J Transplant* 2005; 5(4 Pt 2): 874–886.