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Immunosuppression: practice and trends

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Introduction

The history of solid organ transplantation can be viewed as the history of immunosuppressive strategies. It is not a stretch to divide the record of successful human transplantation into three eras that are characterized by different methods of immunosuppression. In the first of these periods (1954–1962), transplant scientists and clinicians searched for immunosuppressive strategies that would provide modest success and an acceptable level of adverse events. Surgical techniques for engrafting the kidney, liver and later the heart were also issues of experimentation in this period that may be called the 'Experimental Era'. Routine clinical transplantation was confined to identical twins sharing a kidney. The advent of azathioprine in 1962 increased the possibilities for successful human transplants, garnered a Nobel prize for innovative pharmacological progress, and launched a new historical era of organ transplantation, the 'Azathioprine Era'. During this period, kidney transplants could be offered to recipients of organs from living donor sources and even deceased donors with modest success. Graft survival hovered around 50% at 1 year, attended by high rejection rates, but patient survival was strong. Organ transplants could be performed, at least experimentally, in heart and liver recipients. In 1983, the 'Cyclosporine Era' was ushered in by the discovery of cyclosporin A and its provision for clinical use. As has been shown by a recent review of the OPTN/SRTR database, kidney transplant success has become superb, whether evaluated at early time points (1 year) or at later dates (as revealed in graft survival half lives) (1). In this third era, transplantation of extra-renal organs became routine, with excellent outcomes now observed for transplants of livers, pancreata, hearts, and even lungs.

This article analyzes organ transplant history during the most recent decade as a function of immunosuppressive strategies. A careful organ-by-organ review of the OPTN/SRTR data indicates new trends that have arisen as novel molecules have become available for study and wider application. Since 1992, such trends have included the waning of cyclosporine, the rise of induction, the switch to newer cytotoxic agents, and the penetration of even more novel agents. This article will explore just those very trends, which may coalesce into a new historical era of organ transplant.

Unless otherwise noted, the statistics in this article come from reference tables in the *2002 OPTN/SRTR Annual Report*. Two companion articles in this report, 'Data Sources and Structure' and 'Analytical Approaches for Transplant Research', explain the methods of the data collection, organization, and analysis that serve as a basis for this article (2,3).

Kidney Transplantation

Trends in induction therapy

In 1992, the vast majority (91%) of kidney transplant recipients received no induction therapy with antilymphocyte preparations. Of those who did receive induction therapy, most received muromonab-CD3 (OKT3®). The use of induction therapy gradually increased from 1992 to 2001, by which time 59% of recipients received induction. Muromonab-CD3 was the predominant immunosuppressive agent used for induction through 1995. After that

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Note on Sources: The articles in this supplement are based on the reference tables in the *2002 OPTN/SRTR Annual Report*, which are not included in this publication. Many relevant data appear in figures and tables directly referred to in the article; other tables from the Annual Report that serve as the basis for this article include the following: Tables 5.6, 6.6, 7.6, 8.6, 9.6, 10.6, 11.6, 12.6, and 13.6. All of these tables are also available online at http://www.ustransplant.org.

there was increasing use of antithymocyte globulin (ATG)—until the advent of anti-interleukin 2 receptor antibodies, basiliximab (Simulect®) and daclizumab (Zenapax®) in 1998, well-tolerated drugs that were used increasingly through 2001. In 2001, 26% of the 13 109 transplants for which information is available used basiliximab and 15% used daclizumab. Rabbit antithymocyte globulin (Thymoglobulin®) was used in 18% of transplants in 2001, an increase from its introduction in 1999. Muromonab-CD3 use has dropped to <1% of transplants, and ATG use, which peaked in 1997, dropped to 2%.

Immunosuppression therapy prior to discharge

Between 1992 and 2001, nearly all kidney recipients received corticosteroid therapy prior to hospital discharge (Figure 1), although the percentage of recipients receiving corticosteroids toward the end of this period dropped slightly (94% in 2001). Of the other maintenance immunosuppressive drugs used prior to hospital discharge, tacrolimus use grew rapidly in the latter half of the 1990s, being used by 55% of recipients in 2001, while use of cyclosporine-based calcineurin inhibition declined from 94% of recipients in 1992 to 39% in 2001. Antimetabolite use in 1992 was predominantly azathioprine, but by 2001 most transplant centers prescribed mycophenolate mofetil upon discharge. This trend of increasing mycophenolate mofetil use and declining azathioprine use began in 1995 and continued through 2001. Since 1996, rapamycin has also been employed, presumably in an attempt to spare other immunosuppressive drugs, and in particular to reduce the nephrotoxicity of calcineurin inhibitors. By 2001, 17% of transplant recipients received rapamycin upon hospital discharge. Cyclophosphamide (Cytoxan®) was among the other drugs used in the decade, though it was used for only 0.1–0.2% of patients. Of the various cyclosporine preparations, Neoral® use gradually declined from 1996 (59% of all patients) to 2001 (31%). By 2001, there was some increase in generic cyclosporine use, particularly Gengraf® (5%), with a small proportion of the Eon preparation (0.1%). Thus generic cyclosporines have not accounted for much of the declining Neoral usage.

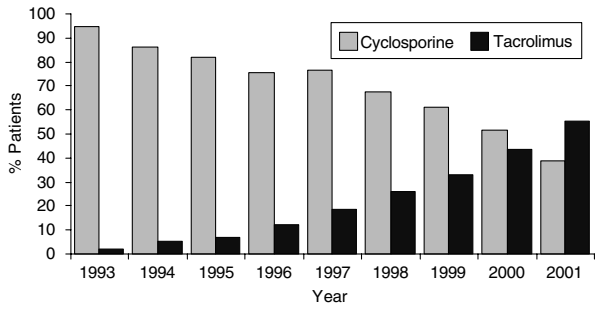

Figure 1: Kidney transplant immunosuppression prior to discharge: cyclosporine vs. tacrolimus, 1993–2001. Source: *2002 OPTN/SRTR Annual Report*, Table 5.6.

Maintenance immunosuppression for first year

For the first year following transplant, the great majority of kidney recipients used a combination of corticosteroids (97% in 2000, compared to 100% in 1992) and a calcineurin inhibitor during the first year. During this 10-year period, cyclosporine use dropped from 96% in 1992 to 53% of the 12 010 transplants done in 2000. There was a corresponding rise in tacrolimus use from 3% in 1992 to 52% in 2000. Thus for both discharge immunosuppression and maintenance through 1 year, the trend is similar, with increasing use of tacrolimus and declining use of cyclosporine in general and Neoral in particular. Similar to the discharge from hospital data, azathioprine use declined from 87% in 1992 to 8% in 2000, while mycophenolate mofetil use increased from 1% to 80%. In 2000, 16% of patients received rapamycin as part of their immunosuppressive medicine. It is not possible to tell the exact combinations used from the data available, and these data give no information about blood level monitoring, protocols, and dose.

Antirejection treatment during first year

In 1992, corticosteroids were used in 81% of antirejection treatment episodes, dropping to 79% in 2000. However, in 2000, only 17% of transplants were followed by treatment for rejection episodes, compared to 38% in 1992. Of the episodes requiring antilymphocyte therapy, muromonab-CD3 was the predominant agent used through 1998, with an increasing use of rabbit antithymocyte globulin beginning in 1999. In 2000, rabbit antithymocyte globulin was used for 14% of the patients, compared to 16% of patients treated with muromonab-CD3. Although daclizumab and basiliximab are neither approved nor recommended for treatment of acute rejection, each was reported to be used in approximately 4% of acute rejection episodes in 2000. The exact sequence and dose regimens are not included in the available data.

The trends toward more tacrolimus replacing cyclosporines are striking. The reasons for this shift are not certain, but may include better correlation of tacrolimus through increasing levels with clinical events, putatively less nephrotoxicity, and marketing practices. Mycophenolate mofetil use may be rising on perception of greater efficacy than azathioprine.

Pancreas Transplantation

Trends in induction therapy

Induction therapy is usually included in immunosuppressive protocols for recipients of whole-pancreas transplants. In fact, induction therapy is used with greater frequency for pancreas transplant recipients than for any other solid-organ recipients. One reason for this is that simultaneous kidney–pancreas (SPK), pancreas after kidney (PAK), and pancreas transplant alone (PTA) recipients all exhibit a higher risk of rejection than recipients of other

solid-organ transplants. The use of induction therapy in pancreas transplantation has generally been guided by practical experience rather than by the results of formal randomized, prospective, multicenter trials. No FDA-approved immunosuppressive agents are on the market with a labeled indication of reducing rejection rates specifically for pancreas transplant recipients. Nonetheless, in 2001, 78% of solitary pancreas (PAK and PTA) transplant recipients and over 75% of SPK transplant recipients received induction therapy. By comparison, recipients of other solid-organ transplants received induction therapy in 2001 in the following proportions: 59% (kidney), 15% (liver), 50% (intestine), 44% (heart), 39% (lung), and 76% (heart–lung).

Over the past 10 years some interesting trends have been observed in the frequency and type of the induction therapy agent used in solitary pancreas and SPK transplant recipients. For solitary pancreas transplant recipients, virtually 100% of the cases of induction therapy from 1994 through 1997 utilized either muromonab-CD3 or ATG. Since 1998, the use of daclizumab, basiliximab, and rabbit antithymocyte globulin has supplanted these. The proportion of solitary pancreas recipients receiving rabbit antithymocyte globulin increased from 0.7% in 1998 to 54% in 2001. The same trend holds true for recipients of SPK transplants. From 1992 to 1997, virtually all cases of induction therapy involved the use of either muromonab-CD3 or ATG. Between 1998 and 2001, basiliximab use rose from 7% to 32%, daclizumab use rose from 15% to 21%, and rabbit antithymocyte globulin use rose from 0.4% to 29%.

When induction therapy is currently used in whole-pancreas transplantation, it is often a T-cell-depleting agent (57% in 2001) and/or an interleukin-2 receptor (IL-2R) antagonist (48% in 2001). For comparison, among recipients of other organ transplants who received induction therapy in 2001, the following proportions received T-cell-depleting induction therapy: 21% (kidney), 4% (liver), 22% (intestine), 28% (heart), 15% (lung), and 40% (heart–lung).

For recipients of solitary pancreas transplants, 395 courses of induction therapy were given to 379 recipients. Many recipients received more than one induction agent—typically rabbit antithymocyte globulin and daclizumab. This strategy is a notable exception to how induction therapy is applied for the other solid organ transplants, including SPK transplantation. In 2001, rabbit antithymocyte globulin was used in slightly more than half of all cases in which induction therapy was applied; daclizumab and basiliximab accounted for 36% and 12% of cases of induction therapy, respectively. For recipients of SPK transplants in 2001, 53% of all induction therapy utilized an IL-2 receptor antagonist (32% basiliximab and 21% daclizumab), and in 36% of cases a T-cell-depleting agent was used (29% rabbit antithymocyte globulin, 4% muromonab-CD3 and 3% ATG).

Immunosuppression therapy prior to discharge

Maintenance immunosuppressive agents used for pancreas transplantation fall into the following categories: (a) corticosteroids, (b) calcineurin inhibitors (cyclosporine and tacrolimus), (c) antimetabolites (azathioprine and mycophenolate mofetil), and (d) other (rapamycin and cyclophosphamide). In 2001, solitary pancreas recipients received corticosteroids in 93% of cases, tacrolimus in 91% (cyclosporine 8%), mycophenolate mofetil in 74% (azathioprine 1%) and rapamycin in 19%. Therefore, in 2001, the most frequently used combination of maintenance therapy at discharge was tacrolimus, mycophenolate mofetil, and corticosteroids.

The dominant use of tacrolimus today represents a marked shift from earlier eras. Tacrolimus was approved for marketing by the FDA for kidney transplantation in 1994. In 1992–93, cyclosporine accounted for virtually 100% of the calcineurin inhibitor use in pancreas transplantation. In 1994, 32% of solitary pancreas recipients received tacrolimus. Its use has increased yearly and reached 91% in 2001. The FDA approved mycophenolate mofetil for marketing for kidney transplantation in 1995, and it was used in only 14% of solitary pancreas transplant cases that year (azathioprine was used in 72% of cases). However, within 1 year, nearly 80% of solitary pancreas transplant recipients received mycophenolate mofetil, with only 12% receiving azathioprine. The use of azathioprine has diminished yearly and dropped to 1% usage in 2001. In 1999, the FDA approved the use of rapamycin for marketing for kidney transplantation. For pancreas transplantation, this agent is usually used in combination with a calcineurin inhibitor, and as a substitute for an antimetabolite. The use of rapamycin has been relatively slow to penetrate the market, compared to the rapid spread of tacrolimus and mycophenolate mofetil usage. In 2000 and 2001, rapamycin was used for 10% and 19% of solitary pancreas cases, respectively.

Similar trends in the use of maintenance immunosuppression were also observed for recipients of SPK transplants. In 2001, 92% of the 820 SPK transplant recipients received corticosteroids, 86% tacrolimus (14% cyclosporine), 82% mycophenolate mofetil, and 19% rapamycin. Based on these data, one can extrapolate that the most common maintenance immunosuppressive regimen used in SPK transplant recipients included corticosteroids, tacrolimus, and mycophenolate mofetil.

Trends in the uses of maintenance therapies over the past 10 years for SPK transplant recipients are depicted in Figures 2 and 3. The use of tacrolimus rose from 17% in 1994 to 86% in 2001. Because tacrolimus is used as a replacement for cyclosporine, cyclosporine usage has dropped from nearly 100% of cases in 1992 to only 14% of cases in 2001. Similar trends in the use of antimetabolites are seen with respect to azathioprine and mycophenolate mofetil. In 1992, azathioprine was used in

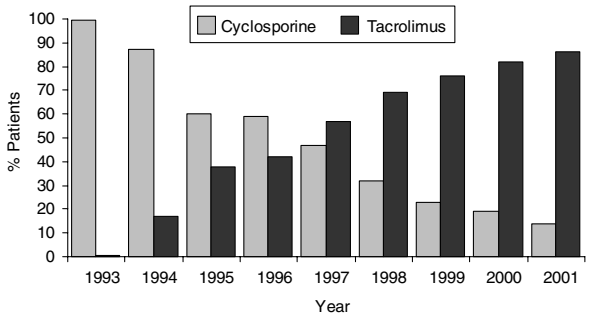

Figure 2: Kidney–pancreas transplant immunosuppression prior to discharge: cyclosporine vs. tacrolimus, 1993–2001. Source: *2002 OPTN/SRTR Annual Report*, Table 8.6.

nearly 100% of cases, dropping to 1% in 2001; mycophenolate mofetil usage grew from 25% in 1995 to 82% in 2001. From 2000 to 2001, rapamycin usage rose from 13% to 19% of cases.

Maintenance immunosuppression for first year

In 1992, over 93% of solitary pancreas transplant recipients received cyclosporine, a percentage that dropped to 15% by 2000. The use of tacrolimus increased from less than 7% in 1992 to over 90% in 2000. Mycophenolate mofetil was not used until 1995, when 59% of cases received it; in 2000, over 83% used it. Rapamycin usage rose from 11% in 1999 (its first year of marketing) to 24% in 2000. Similar trends in the escalating use of tacrolimus and mycophenolate mofetil and the declining use of cyclosporine and azathioprine among SPK transplant recipients were also exhibited. In 1992, virtually 100% of SPK transplant recipients received cyclosporine; by 2000, less than 25% received it. The use of tacrolimus increased from essentially 0% in 1992 to 84% in 2000. Mycophenolate mofetil usage nearly doubled from 44% in 1995 to 86% in 2000. Azathioprine has all but disappeared from use, dropping from 96% of cases in 1992 to 6% in 2000. Rapamycin use rose from 4% in 1999 to 20% in 2000.

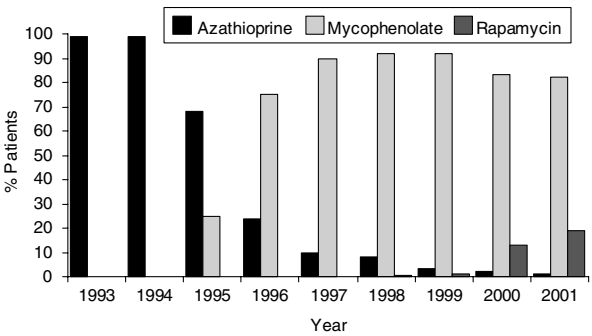

Figure 3: Kidney–pancreas transplant immunosuppression prior to discharge: azathioprine, mycophenolate mofetil, and rapamycin, 1993–2001. Source: *2002 OPTN/SRTR Annual Report*, Table 8.6.

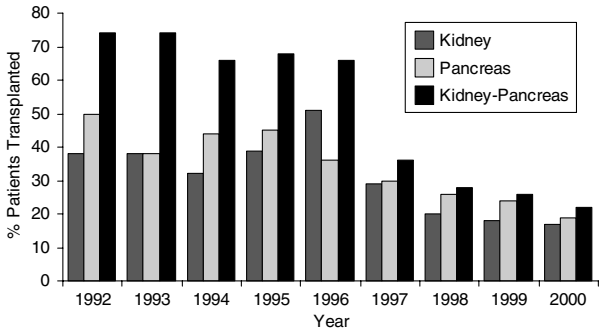

Figure 4: Incidence of rejection at 1 year in kidney, pancreas, and kidney–pancreas transplant recipients, 1992–2000. Source: *2002 OPTN/SRTR Annual Report*, Tables 5.6, 6.6, 7.6, 8.6.

Antirejection treatment during first year

It is interesting to note that from 1992 to 2000 the incidence of rejection during the first year decreased dramatically for solitary pancreas (PAK and PTA) as well as SPK recipients (Figure 4). For recipients of solitary pancreas transplants, the proportion of patients reported to receive antirejection therapy in 1992 was 50%, though this may be an underrepresentation of the true proportion that actually experienced a rejection episode. By 2000, only 19% were reported to have received antirejection therapy during the first year. Similar trends are noted for the SPK transplant recipients (74% in 1992, 22% in 2000). For comparison, kidney-alone transplant recipients required antirejection treatment in 38% of cases in 1992 and 17% of cases in 2000.

The type of antirejection agent used for treatment of rejection entailed the individual or combined use of corticosteroids or T-cell-depleting agents. In 2000, the use of corticosteroids was the most frequently employed antirejection agent among solitary pancreas transplant recipients (85%) and SPK transplant recipients (80%). In 2000, recipients of a solitary pancreas transplant received T-cell-depleting agents in 80% of cases; the specific agents used were either muromonab-CD3 (45%) or rabbit antithymocyte globulin (34%). For recipients of SPK transplants, T-cell-depleting agents were given in 48% of cases; the two most frequently used T-cell-depleting agents were muromonab-CD3 (27%) and rabbit antithymocyte globulin (17%). Compared to kidney-alone transplant recipients, pancreas transplant recipients received more treatments with T-cell-depleting agents for treatment of rejection. In 2000, kidney alone transplant recipients received an anti-T-cell-depleting agent in 38% of cases.

Trends in T-cell antibody antirejection therapy usage over the past 10 years in both solitary pancreas and SPK transplant recipients show that muromonab-CD3 is still the most commonly used agent. The use of rabbit antithymocyte globulin has progressively increased since 1998, and

the use of the other antilymphocyte globulins has diminished significantly.

Liver Transplantation

Trends in induction therapy

The use of induction therapy for liver transplant recipients utilizing polyclonal antilymphocyte antibody preparations (ALG) or muromonab-CD3 peaked in 1995, at which time 10% of the 3365 liver recipients for whom immunosuppression data were available were treated with muromonab-CD3, a percentage that declined progressively through 2001. The use of these two products for induction has essentially been replaced by the chimeric and humanized anti-IL-2R monoclonal antibody preparations (basiliximab and daclizumab), each of which were selected for approximately 6% of the 4812 liver recipients in 2001. Rabbit antithymocyte globulin has been utilized infrequently in recent years (2% in 2001).

Immunosuppression therapy prior to discharge

There has been some recent enthusiasm for steroid-avoidance regimens in selected liver transplant recipients (4,5). Over the last 4 years, there has been a small but progressive decline in the use of either prednisone or prednisolone for maintenance immunosuppression prior to discharge. By 2001, more than 11% of patients were discharged on steroid-free regimens. Steroid-avoidance protocols have often incorporated anti-IL-2R monoclonal antibody or polyclonal ATG induction therapy (4,5), both of which were utilized with increasing frequency during this same period. Calcineurin inhibitors remained the backbone of early maintenance therapy throughout the 10-year period of review. From 1992 to 2001, 94–100% of patients were receiving either cyclosporine or tacrolimus prior to discharge. However, tacrolimus has replaced cyclosporine as the principal calcineurin inhibitor for maintenance therapy (Figure 5).

The introduction of Neoral did not appear to have a significant impact upon this latter trend. Generic cyclosporine preparations became available during 2000 and 2001 and accounted for fewer than 10% of the liver recipients receiving a cyclosporine-based regimen, or approximately 1% of all patients at discharge. Antimetabolite therapy was utilized in approximately 40–60% of patients over the 10-year study, and there did not seem to be a definable trend in total usage. The selection of specific antimetabolic agent, however, is remarkable for replacement of azathioprine with mycophenolate mofetil (Figure 6). In 1993, 58% of liver transplant recipients received azathioprine for maintenance therapy, compared to 3% in 2001, while mycophenolate mofetil usage increased consistently since its introduction and was prescribed prior to discharge for 48% of patients by 2001.

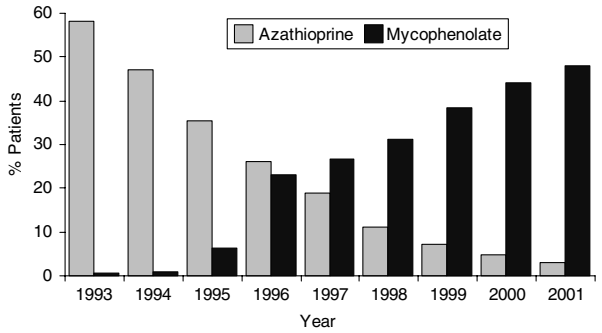

Figure 6: Liver transplant immunosuppression prior to discharge: azathioprine vs. mycophenolate mofetil, 1993–2001. Source: *2002 OPTN/SRTR Annual Report*, Table 9.6.

Antirejection treatment during first year

As Figure 7 indicates, the incidence of graft rejection requiring treatment during the first year postliver transplant declined over the last decade (1435 cases in 2000). Similarly, the incidence of steroid-resistant rejection (i.e. rejection episodes requiring antibody therapy for rescue) has decreased. In 1992–93, muromonab-CD3 was prescribed for approximately one-third of all liver recipients with rejection episodes, compared to 6% in 2000 (Figure 8).

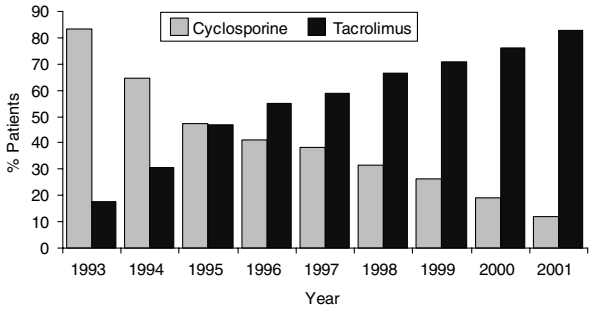

Figure 5: Liver transplant immunosuppression prior to discharge: cyclosporine vs. tacrolimus, 1993–2001. Source: *2002 OPTN/SRTR Annual Report*, Table 9.6.

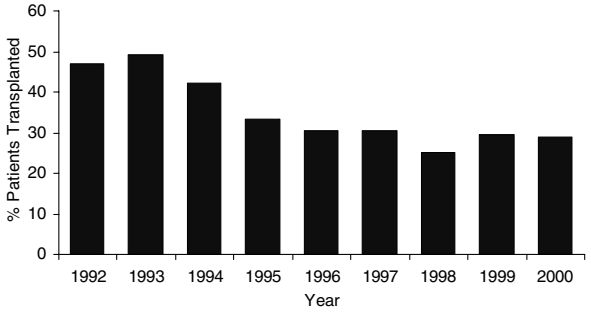

Figure 7: Incidence of rejection at 1 year in liver transplant recipients, 1992–2000. Source: *2002 OPTN/SRTR Annual Report*, Table 9.6.

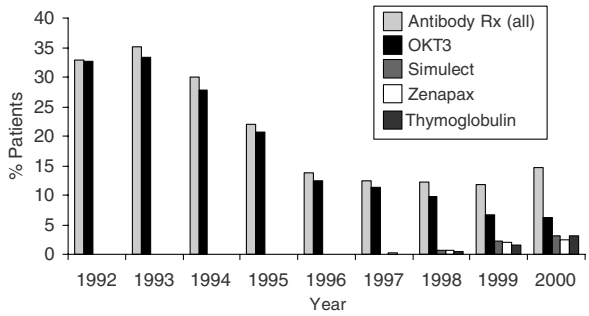

Figure 8: Use of antibody therapy for rejection episodes following liver transplantation, 1992–2000. Source: *2002 OPTN/SRTR Annual Report*, Table 9.6. Note: Many of the original data collection forms (and, therefore, the OPTN/SRTR database) list brand names for drugs rather than generic names.

This trend may be related, in part, to alterations in maintenance therapy instituted over the past decade (e.g. replacement of cyclosporine with tacrolimus as the primary calcineurin inhibitor) (6–8). The decline in muromonab-CD3 use has been accompanied by increases in anti-IL-2R products as well as rabbit antithymocyte globulin. Basiliximab, rabbit antithymocyte globulin, and daclizumab have all been used with increasing frequency to treat rejection over the past several years; each was used for approximately 3% of rejection episodes in 2000 (Figure 9). For those recipients who developed rejection episodes, the utilization of steroids did not change appreciably from 1992 (92%) to 2000 (90%).

Intestine Transplantation

Trends in induction therapy

The interpretation of induction therapy trends in intestine transplant recipients is limited by the relatively small number of patients and incomplete reporting information in recent cohorts. Over the years 1999, 2000, and 2001, immunosuppression information was not available for 24%, 19%, and 18% of the 71, 79, and 111 intestine recipients, respectively. Nonetheless, with the availability of daclizumab in 1998, the use of antibody preparations for induction therapy increased substantially. In 1999, 2000 and 2001, some form of antibody induction was employed in 56% of 54 recipients, 67% of 64 recipients and 50% of 91 recipients, respectively, compared to only 8% of the 64 recipients in 1997. The most frequently selected preparation over the past 3 years has been daclizumab.

Immunosuppression therapy prior to discharge

Although a small number of intestine transplant recipients have been maintained on cyclosporine, the overwhelming majority have been placed on tacrolimus. This trend has not changed over time. Tacrolimus was selected for 100% of the 16 patients in 1992, 92% of 24 in 1996, and 97% in 2001 (information available for 76 patients). Corticosteroids were regularly used for nearly all patients until 2001, when steroid administration prior to discharge fell from 98% to 76%. This drop may be related, in part, to reports by Shapiro and others in which steroids were successfully withdrawn in pediatric intestine transplant recipients (9). Rapamycin, which was not used in 1998 or 1999, was used in 44% of patients in 2000. However, the addition of rapamycin as a maintenance therapy agent could not directly account for the decline in steroids in 2001, since rapamycin usage fell to 14% that year. Antimetabolites, used in over 50% of patients during 1996 and 1997, have fallen out of favor since that time. Mycophenolate mofetil was utilized in 44% of recipients in 1997, but only 3% of patients in 2001 (see Figure 10). The gastrointestinal toxicity of mycophenolate mofetil, as well as concerns regarding the development of tissue-invasive cytomegalovirus virus infections and post-transplant lymphoproliferative disorders, may have played a role in this trend (10,11).

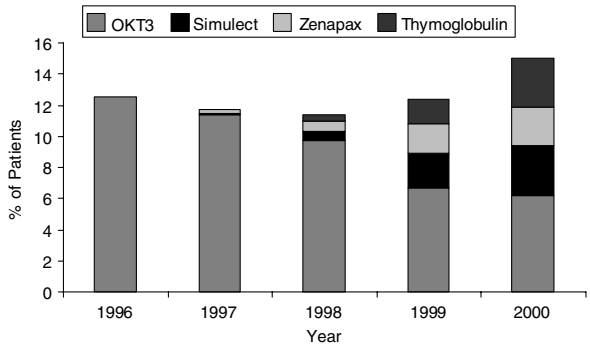

Figure 9: Trends in antibody therapy for rejection episodes following liver transplantation, 1996–2000. Source: *2002 OPTN/SRTR Annual Report*, Table 9.6. Note: Many of the original data collection forms (and, therefore, the OPTN/SRTR database) list brand names for drugs rather than generic names.

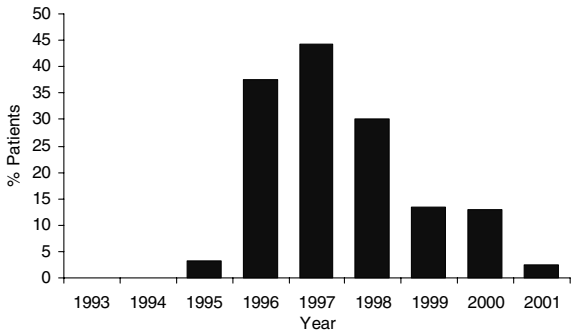

Figure 10: Intestine transplant immunosuppression prior to discharge: use of mycophenolate mofetil, 1993–2001. Source: *2002 OPTN/SRTR Annual Report*, Table 10.6.

Antirejection treatment during first year

In intestine transplant recipients, the incidence of graft rejection requiring treatment during the first year declined from more than three-quarters of 22 patients in 1992 to less than one-half of 79 patients in 2000 (Figure 11). The most dramatic drop was noted from 1997 to 1998, when the incidence of treated rejection fell from 68% to 33%. This decline correlates with modifications made to the induction therapy regimens in intestine transplantation, specifically the use of daclizumab, which was not used at all in 1997, but was used in 37% of recipients in 1998. There were no other major changes in maintenance immunotherapy during this same period.

Heart Transplantation

Trends in induction therapy

The use of antilymphocyte antibody induction for heart transplantation increased over the past 10 years, from 9% of 2152 in 1992 to 44% of 2058 in 2001. In the past decade, muromonab-CD3 and ATG combined accounted for the majority of the induction used, ranging from 9% of all recipients in 1992 to 36% in 1994. Since 1994, the choice of these agents for induction slowly declined such that by 2001, the use of muromonab-CD3 and ATG for induction was down to 16% of induction cases. In contrast, rabbit antithymocyte globulin became more popular over the last 3 years, accounting for 3% of antibody induction in 1999 and increasing to 11% in 2001. In addition, the use of the anti-IL-2 receptor antibodies (daclizumab and basiliximab) for induction increased over the last four years. In 1998, 1% of recipients received induction with the anti-IL-2 receptor inhibitors, compared to 18% in 2001. The use of the anti-IL-2 receptor antibodies exceeded the use of ATG and muromonab-CD3 for induction in 2001. Daclizumab accounted for the majority of the anti-IL-2 receptor antibody used in 2001, and represented 13% of all recipients.

Immunosuppression therapy prior to discharge

From 1992 to 2001, the use of corticosteroids for heart transplantation prior to discharge from the hospital remained relatively unchanged, ranging from 94% to 97%. The use of cyclosporine declined over the same period. In 1992, 98% of heart transplant recipients were discharged from the hospital on cyclosporine, compared to only 71% in 2001. Between 1992 and 1995, the majority of recipients (83–98%) were on Sandimmune. In 1995, 4% of heart transplant recipients were discharged from the hospital on Neoral, with a substantial increase in 1996 to 58%. From 1997 to 2000, Neoral use remained fairly constant at approximately 72% of all recipients, falling in 2001 to 59%. In 2001, 8% of heart transplant recipients were discharged on Gengraf and only 4% of recipients were discharged on Sandimmune.

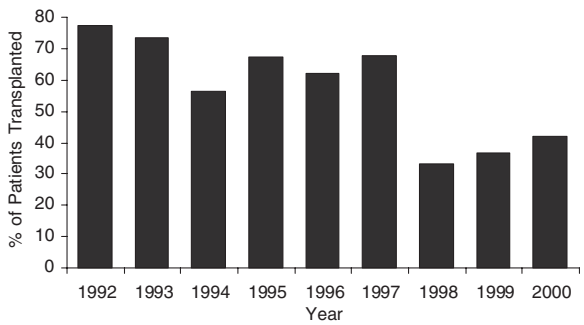

Figure 11: Incidence of rejection at 1 year in intestine transplant recipients, 1992–2000. Source: *2002 OPTN/SRTR Annual Report*, Table 10.6.

Aside from the use of generic cyclosporine preparations, part of the decline in Neoral use at discharge can be attributed to the use of tacrolimus, whose use at discharge increased from 0.6% in 1993 to 29% in 2001.

The use of antimetabolites (azathioprine and mycophenolate mofetil) at discharge remained fairly consistent and very common over the last 10 years, ranging from 82% to 96%. The use of azathioprine dropped sharply over the same period, from 95% in 1992 to 15% in 2001. Conversely, mycophenolate mofetil use at discharge increased dramatically, rising from 0.6% in 1993 to 79% in 2001.

Cyclophosphamide use at discharge remained at a low level over the study period, ranging from 0.5% to 1.4%. On the other hand, the use of rapamycin has slowly increased, climbing from 0.1% in 1998 to 4% in 2001.

Maintenance immunosuppression for first year

The majority (88–96%) of heart transplant recipients were on corticosteroids 1 year after transplantation, similar to the time of discharge.

The use of cyclosporine for maintenance immunosuppression declined from 99% in 1992 to 78% in 2000. In 2000, 69% of recipients were using Neoral, with 5% each on Gengraf and Sandimmune. Maintenance use of tacrolimus rose steadily since 1992, when only 1% of recipients used it 1 year post-transplant; 30% used it in 2000.

Over the last 9 years, antimetabolites have been used somewhat less often for maintenance immunosuppression than initially at discharge, ranging from 86% to 97%. The percentage of patients on mycophenolate mofetil steadily increased from 17% in 1995 to 79% in 2000. Conversely, the percentage of patients maintained on azathioprine dropped from 97% in 1992 to 19% in 2000. The use of cyclophosphamide for maintenance immunosuppression also dropped, drifting downward slightly from 2% in 1992 to 0.7% in 2000. Rapamycin use rose from 0.1% in 1997 to 5% in 2000.

In 2000, the most common maintenance therapy combination for heart transplant recipients consisted of

corticosteroids, cyclosporine (Neoral) or tacrolimus, and mycophenolate mofetil.

Antirejection treatment for first year

Approximately 40% of heart transplant recipients receive antirejection treatment and this figure remained fairly constant from 1992 to 2000, dipping slightly in 1996 and 1997.

Regardless of the year of transplantation, the majority of heart transplant recipients received corticosteroids as part of their antirejection treatment regimen. The distribution of corticosteroid use for the treatment of rejection ranged from 88% to 92%.

In 2000, 16% of the 2197 heart transplant patients received antibody therapy to reverse a rejection episode. The highest percentage of patients to receive antibody treatment for rejection was 26% (in 1993). The use of muromonab-CD3 to treat rejection has declined over the years. In 1992, 22% of the 2126 heart transplant recipients received muromonab-CD3 for antirejection treatment, compared to 5% in 2000. The use of ATG for the treatment of rejection ranged from 4% to 7% (except for 1992, when its use was only 0.8%). The use of rabbit antithymocyte globulin has been increasing since 1997, rising from 0.1% to 4% in 2000. In 2000, a small percentage of patients (5%) were reported to have received anti-IL-2 receptor antibody for the treatment of rejection.

In conclusion, corticosteroids, used for maintenance or rejection, continue to play a major role in immunosuppression for heart transplantation. In recent years, the use of tacrolimus for maintenance immunosuppression has increased. This trend can also be seen with mycophenolate mofetil. To date, rapamycin has had only a minor role in the maintenance immunosuppression for heart transplantation. Induction has increased over the last decade (34%) and has slowly involved the use of newer agents such as rabbit antithymocyte globulin and the anti-IL-2 receptor antibodies. The use of muromonab-CD3 to treat rejection has declined over the years, with 4% of patients in 2000 receiving rabbit antithymocyte globulin to treat heart rejection.

Lung Transplantation

Trends in induction therapy

Since 1992, the use of induction therapy for lung transplantation has increased from 5% (of 531) to 39% (of 1009) in 2001, with a peak of 43% in 2000. The largest increase occurred between 1993 (3%) and 1994 (25%). The majority of induction in 2001 consisted of polyclonal antibodies (14%) and anti-IL-2 receptor antibodies (25%).

Before 1998, ATG and muromonab-CD3 were the agents used for induction in lung transplantation. The percentage of lung transplant recipients who received ATG peaked in 1995 at 23%. Since that time, the use of ATG has slowly declined, dropping to 9% in 2001. The use of muromonab-CD3 for induction in lung transplantation has remained fairly low over the last 9 years, ranging from 1% to 6%.

Since 1998, newer agents have been used for induction therapy in lung transplantation. Among lung transplants performed in 1998, 3% of recipients received induction with daclizumab. In 2000, the use of daclizumab for induction therapy increased to 14%. In addition, in 1999, basiliximab and rabbit antithymocyte globulin began to be used for induction in lung transplantation. From 1999 to 2001, the use of basiliximab increased from 2% to 14% and that of rabbit antithymocyte globulin from 2% to 6% of patients.

Immunosuppression therapy prior to discharge

From 1992 to 2001, the use of corticosteroids in lung transplantation remained relatively unchanged. In 1992, 96% of lung transplant recipients were on corticosteroids prior to discharge. In 2001, the percentage was 99%. The use of cyclosporine prior to discharge declined slowly over this period. In 2001, 51% of lung transplant recipients were discharged from the hospital on cyclosporine, compared to 92% of recipients in 1994. Conversely, use of tacrolimus prior to discharge has been steadily rising. In 2001, 50% of lung transplant recipients received tacrolimus, compared to 6% in 1992. Earlier in the decade, the majority of lung transplant recipients were discharged from the hospital on Sandimmune. In contrast, 0.5% of lung transplant recipients were discharged on Neoral in 1994, around the time of its introduction, a percentage that rose markedly by 1996 to 49%. The use of Neoral prior to discharge peaked in 1998 at 64% and declined to 40% in 2001. Gengraf use prior to discharge was at 1% in 2000 and 6% in 2001.

The overall use of antimetabolites (azathioprine and mycophenolate mofetil) prior to discharge for lung transplant recipients remained fairly constant and widespread over the last decade, ranging from 90% in 1996 to 98% in 1993. The use of azathioprine declined from 98% in 1993 to 51% in 2001, while mycophenolate mofetil use increased from 0.3% in 1994 to 43% in 2001.

The use of cyclophosphamide in lung transplantation prior to discharge from the hospital also remained low over the last decade, ranging from 0.1% in 1995 to 0.4% in 2000. Rapamycin has gained some favor in lung transplantation prior to discharge, rising from 0.1% in 1997 to 4% in 2001.

Maintenance immunosuppression for first year

Nearly all lung transplant recipients (98–100%) were on corticosteroids 1 year after transplantation between 1992 and 2000.

The use of cyclosporine for maintenance immunosuppression for lung transplant recipients declined from 93% in 1992 to 54% in 2000. Conversely, the use of tacrolimus

increased over the last 9 years, from 7% in 1992 to 56% in 2000. Whereas cyclosporine (Sandimmune) dominated maintenance immunosuppression earlier, use of Neoral increased over the years, rising from 2% in 1994 to 59% in 1998. In 2000, 49% of lung transplant recipients were maintained on Neoral and 3% of lung transplant recipients were maintained on Gengraf.

Similar to immunosuppression prior to discharge, the use of azathioprine for maintenance immunosuppression in lung transplantation has declined over the last 9 years, dropping from 97% in 1993 to 54% in 2000. Mycophenolate mofetil use increased from 0.2% to 49% over the same period. The majority (88–97%) of lung transplant recipients were maintained on at least one antimetabolite over the last 9 years.

The use of cyclophosphamide as maintenance immunosuppression in lung transplantation remained under 0.8%. The use of rapamycin in maintenance immunosuppression rose from 0.2% in 1998 to 6% in 2000.

Overall in 2000, the majority of lung transplant recipients were maintained on corticosteroids, calcineurin inhibitors, and antimetabolites with more lung transplant recipients being maintained on mycophenolate mofetil and tacrolimus than in previous years.

Antirejection treatment for first year

Over the last 9 years, 42–56% of lung transplant recipients have received antirejection treatment during the first post-transplant year. Regardless of the year, the majority of lung transplant recipients received corticosteroids as part of their antirejection treatment. The distribution of corticosteroid use ranged from 88% to 97%.

The use of antibodies to treat rejection in lung transplantation has varied over the last 9 years. The percentage of lung transplant recipients who received antibodies ranged from 9% in 1992 to 19% in 2000. Over this period, the majority of rejection episodes in lung transplant patients were treated with muromonab-CD3 and ATG, although the use of these agents has declined in recent years. The use of ATG to treat rejection in lung transplantation ranged from 0.8% in 1992 to 10% in 1994 to 7% in 1999. In 1994, a small percentage of patients (1%) received ALG for lung transplant rejection. The use of muromonab-CD3 has declined over the years, dropping from 8% in 1992 to 3% in 2000. Since 1998, rabbit antithymocyte globulin, daclizumab, and basiliximab have been used to treat lung transplant rejection. The use of rabbit antithymocyte globulin ranged from 0.8% in 1998 to 6% in 2000. The use of daclizumab and basiliximab both ranged from 0.3% in 1998 to approximately 3% in 2000.

To sum up: corticosteroids remain the mainstay of immunosuppression in lung transplantation. In contrast with previous years, the majority of lung transplant recipients are now initiated and maintained on tacrolimus. The use of mycophenolate mofetil has also increased over the last few years; only a small percentage of lung transplant recipients received rapamycin as maintenance immunosuppression. The use of the anti-IL-2 receptor antibodies has increased in recent years, both for induction and rejection. In contrast, muromonab-CD3 has had only marginal use for induction and rejection in lung transplantation and, in recent years, the use of ATG has declined.

Heart–Lung Transplantation

Trends in induction therapy

The use of induction for heart–lung transplantation increased from 6% (of 46 total) in 1992 to 76% (of 25 total) in 2001. Muromonab-CD3 and ATG accounted for the majority of induction used between 1992 and 1998. The use of muromonab-CD3 for induction in heart–lung transplantation remained relatively stable between 6% and 12%. The use of ATG for induction ranged from 10% to 44%. In recent years, three other drugs have been used increasingly for induction in heart–lung transplantation: rabbit antithymocyte globulin (4% in 1999, 12% in 2001), daclizumab (4% in 1999, 8% in 2001), and basiliximab (4% in 2000, 32% in 2001). In 2001, the use of anti-IL-2 receptor antibodies and polyclonal antibodies for induction in heart–lung transplantation was about 40% each.

Immunosuppression therapy prior to discharge

From 1992 to 2001, the use of corticosteroids prior to discharge after heart–lung transplantation remained relatively widespread and stable, ranging from 88% to 100%. The use of calcineurin inhibitors varied more widely over the same period. The use of cyclosporine was as low as 63% in 1999 and as high as 91% earlier in the decade. The use of Sandimmune prior to discharge was predominant in the early 1990s, but in 1996 was surpassed by Neoral, which rose to a high of 71% in 2000. In 2000 and 2001, the use of Gengraf for heart–lung transplant recipients at discharge was only 3% and 5%, respectively. The use of tacrolimus varied widely during the period, ranging from 2% to 40%.

The use of antimetabolites remained between 83% and 96%. The use of azathioprine dropped from 95% in 1992 to 45% in 2001. In contrast, the use of mycophenolate mofetil rose from 2% in 1995 to 50% in 2001.

More than 94% of heart–lung transplant recipients were on corticosteroids and antimetabolites prior to discharge (roughly split between azathioprine and mycophenolate mofetil). In 2001, 20% of recipients were discharged on tacrolimus and 75% were discharged on cyclosporine.

Maintenance immunosuppression for first year
In keeping with immunosuppression usage prior to discharge, nearly all (96–100%) heart–lung transplant recipients were on corticosteroids 1 year after transplantation.

The use of cyclosporine for maintenance immunosuppression in heart–lung transplantation has varied (56–93%) over the last 9 years. Neoral replaced Sandimmune as the dominant maintenance immunosuppression, Neoral peaking in 1998 at 65%. In 2000, 7% of heart–lung transplant recipients were on Gengraf and 57% were on tacrolimus.

Similar to its usage prior to discharge, antimetabolite usage in heart–lung transplant recipients 1 year after transplantation changed little (82–97%) from 1992 to 2000. The use of azathioprine for maintenance immunosuppression declined from 97% in 1992 to 43% in 2000. Conversely, the use of mycophenolate mofetil rose from 2% in 1994 to 64% in 2000. In 2000, more heart–lung transplant recipients were maintained on tacrolimus (57%), mycophenolate mofetil (64%), and rapamycin (11%) than earlier in the decade.

Antirejection treatment for first year
The percentage of heart–lung transplant recipients who have received antirejection treatment within a year of transplantation has varied from 20% to 53% over the last 9 years. Regardless of the year, most (80–100%) received corticosteroids as part of their antirejection regimen. Over the same period, the use of antibodies has ranged from 6% to 20%. The use of muromonab-CD3 to treat rejection declined from 12% in 1993 to no use in recent years. The use of ATG was variable (12% in 1993 and 1998, none in 1999), as was the use of rabbit antithymocyte globulin (4% in 1998 and 6% in 1999). Interestingly, 12% of heart–lung rejection episodes in 2000 were reported to have been treated with daclizumab, an anti-IL-2 receptor antibody.

In conclusion, most of the small number of heart–lung transplant recipients were on corticosteroids for maintenance immunosuppression; at times, 100% of the recipients received corticosteroids for rejection. Although most heart–lung recipients were initiated on cyclosporine, many were maintained on tacrolimus. In recent years, mycophenolate mofetil has dominated both initial and maintenance immunosuppression. Recently, rabbit antithymocyte globulin and the anti-IL-2 receptor antibodies have been used for induction in heart–lung transplantation. These two agents remained options for antirejection treatment, as did muromonab-CD3.

Comparison of Organs

Trends in induction therapy
The percentage of patients receiving induction therapy varied widely among transplanted organs. Pancreas, kidney–pancreas and heart–lung transplant recipients most often received induction therapy, with the use of at least one agent reported in more than 70% of these transplants in 2001. Between 40% and 60% of kidney, intestine, heart, and lung transplant recipients, and fewer than 20% of liver transplant recipients, received induction therapy.

A switch from ATG or muromonab-CD3 as the primary induction agent to rabbit antithymocyte globulin, daclizumab or basiliximab occurred in 1998 for intestine, in 1999 for kidney, pancreas, kidney-pancreas, liver, in 2000 for heart and lung, and in 2001 for heart–lung recipients. In 2001, basiliximab was the most widely used induction agent for kidney, kidney–pancreas, lung and heart–lung transplants, rabbit antithymocyte globulin for pancreas, and daclizumab for intestine and heart transplants.

Trends in immunosuppression therapy prior to discharge
Drug regimens used for maintenance immunosuppression at discharge varied widely by transplanted organ. Most notable was the wide variation in the choice of calcineurin inhibitor. Tacrolimus has always been the predominant agent for intestinal transplants, and its use surpassed that of cyclosporine formulations for pancreas transplants in 1995, liver in 1996, kidney–pancreas in 1997, and kidney and lung transplants in 2001. Neoral remains the predominant calcineurin inhibitor in heart and heart–lung transplants.

Corticosteroids were widely used in over 95% of cases for pancreas, heart, lung and heart–lung recipients in 2001. Between 75% and 90% of liver and intestine transplant recipients received corticosteroids. Prednisone was the predominant corticosteroid administered to more than 80% of recipients—except for intestine transplants, of whom 43% received prednisone and 33% received methylprednisolone.

Antimetabolites were reported for more than 90% of heart, lung and heart–lung transplants, 75–90% of kidney, pancreas, and kidney-pancreas transplants, and fewer than 60% of liver and intestine transplants in 2001. Mycophenolate mofetil replaced azathioprine as the predominant antimetabolite agent in 1996 for kidney, pancreas, kidney–pancreas, and intestine transplants, in 1997 for liver transplants, in 1999 for heart transplants, and in 2001 for heart–lung transplants. Azathioprine has remained the predominant antimetabolite for lung transplants. In 2001, rapamycin was administered to more than 10% of kidney, pancreas, kidney-pancreas, and intestine transplant recipients.

Trends in antirejection treatment for first year
There has been a downward trend in the percentage of recipients with antirejection treatment noted in the first post-transplant year for most types of transplant (Figure 12). In 1992, over 70% of kidney–pancreas and intestine transplants, 50% of pancreas, liver, and lung transplants,

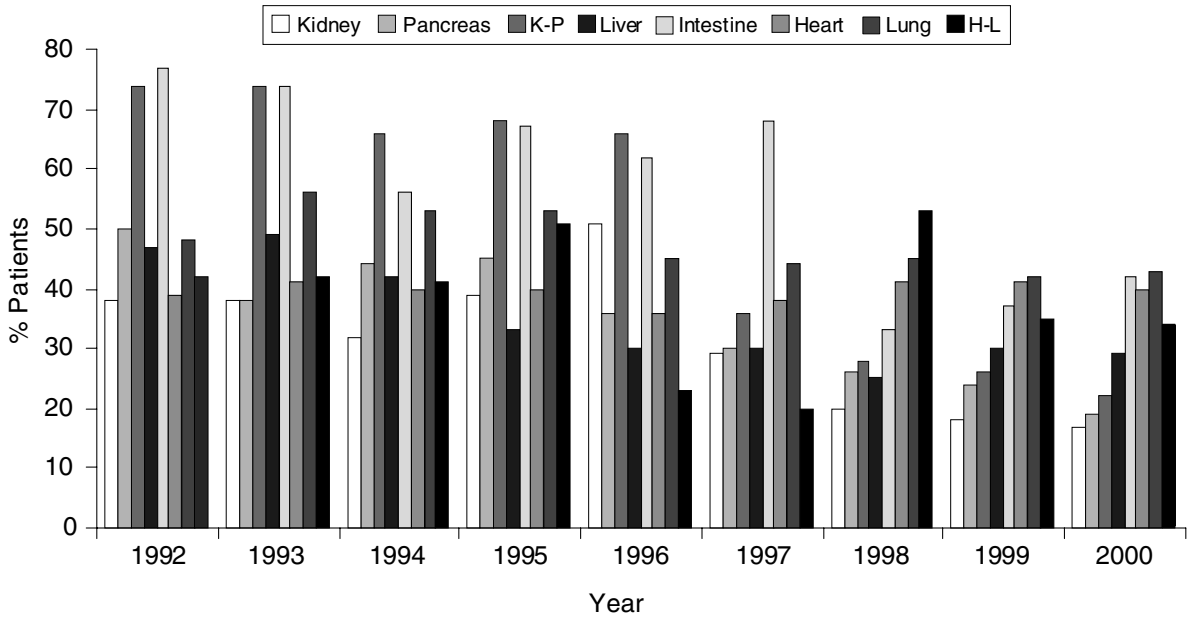

Figure 12: Percentage of recipients with antirejection treatment by year of transplant, 1992–2000. Source: *2002 OPTN/SRTR Annual Report*, Tables 5.6, 6.6, 7.6, 8.6, 9.6, 10.6, 11.6, 12.6, 13.6.

and 40% of kidney, heart, and heart–lung transplants were treated for rejection. In 2000, the percentage of kidney, pancreas, and kidney–pancreas transplants with reported rejection treatment decreased to approximately 20%, and rejection treatments for liver transplants dropped to 30%. Interestingly, the percentage of heart, lung and heart–lung transplants treated for rejection remained at about 40%.

Corticosteroids were the most common treatment for rejection reported for more than 85% of pancreas, liver, intestine, heart, lung and heart–lung transplants and 75–85% of kidney and kidney–pancreas transplants. Methylprednisolone was the predominant steroid agent (55–85%) reported for all organs.

Antilymphocytic therapy was most often administered in pancreas transplants (70%), but was also administered in 35–50% of kidney, kidney–pancreas and intestine transplants, and in less than 20% of liver, heart, lung and heart–lung transplants.

Conclusion

An organ-by-organ review of the use of immunosuppression supports the concept that the transplant community has entered a new historic era in the discipline. The 'Experimental Era' (1954–62) was characterized by limited transplantation and an assiduous search for acceptable immunosuppression techniques. The 'Azathioprine Era' (1962–83) extended transplantation to a wider variety of patients and organs with a homogenous protocol and more acceptable (though not wonderful) outcomes. The 'Cyclosporine Era' (1983–95) was characterized by an important improvement in outcomes and the routine of transplantation of extra renal organs, also with a relatively fixed regimen. A review of the trends in organ transplant management that has been the subject of this contribution has unambiguously demonstrated that the one-size-fits-all approach to transplant management is over.

Induction therapy with antilymphocyte preparations or anti-IL-2R antibodies has become an increasingly common strategy for all organ transplants. There has been an important shift away from cyclosporine toward tacrolimus as the calcineurin inhibitor of choice. Mycophenolate mofetil has become the predominant cytostatic adjunct, while rapamycin is beginning to penetrate use patterns. Protocols have emerged that mix and match the therapeutic options available for specific characteristics of each recipient and organ. This shift of agent signals a strategy that emerged toward the end of this review period: the attempt to achieve the same excellent graft and patient outcomes with the fewest and least toxic of regimens.

This review suggests that the transplant community has entered an 'interregnum' period marked by a flurry of new drug development and clinical research. It is our expectation that as newer agents and strategies take hold, their effects will keep pace with the growing need for flexible and effective therapies. Future monitoring of trends in immunosuppression will provide a lens to detect these new themes and approaches, as this review of the past decade has revealed the end of one period and the birth of a new one.

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