CHAPTER IV
Immunosuppression Practice and Trends

INTRODUCTION

This chapter analyzes solid organ transplantation over the 10-year time span of 1993 to 2002. This period has been distinguished by marked changes in the clinical practice of transplantation, in general, and in immunosuppressive strategies, in particular. Certain aspects of the evolutionary changes of immunotherapeutics are captured quite nicely by the OPTN/SRTR data. Particularly strong components include the scale and pace by which the new immunosuppressive molecules and antibodies have become incorporated into the daily activities of transplant medicine. A careful organ-by-organ review of the data indicates how much has changed over the 10-year span beginning in 1993.

Regarding the use of maintenance immunosuppression, practice patterns indicated a strong role of calcineurin inhibitor-based immunosuppression. Yet this was occurring during a time when the availability of generic versions of cyclosporine was expanding and the collective use of cyclosporines, generally, was rapidly diminishing. In its place has been a sustained transition to the use of tacrolimus. Similar trends were also observed with the anti-metabolites azathioprine and mycophenolate mofetil — the latter being used in the vast majority of transplant recipients. Recent years have seen the advent of the novel agent rapamycin, although its use has not mimicked the rapid and consistently successful incorporation of tacrolimus and mycophenolate mofetil. This may be indicative of uncertainty regarding its role in maintenance immunosuppression in organ transplantation at this juncture.

One practice trend in the use of maintenance immunotherapy that is not clearly elucidated by the data is the intensity of the immunosuppression. In one respect, it could be concluded that overall intensity has increased. Evidence of this viewpoint could be derived from increased use of the potent agents tacrolimus, mycophenolate mofetil, and rapamycin. From another perspective, there are clues that efforts are ongoing with aims of immunosuppression minimization. A hint of that is suggested by the subtle changes in the reduced application of chronic corticosteroid therapy. A more precise assessment could be deduced knowing the relative dosing schedules of the individual agents. Unfortunately, one of the limitations of the data is that it is relatively qualitative in nature. Specifics regarding the pharmacologic exposure of the recipients to the individual agents are understandably beyond the SRTR aims at this time.

Regarding antibody-based induction therapy, practice patterns indicate that its use and intensity are rising each year. There are consistent trends indicating a switch to T-cell depleting agents, especially rabbit antithymocyte globulin. However, the lack of quantitative data regarding the actual dosing and duration of therapy does not allow trends to be determined in that context. Use of alemtuzumab (Campath®) induction therapy (as an alternative T-cell depleting agent) and rituximab (Rituxan®) immunotherapy (used in antibody desensitization protocols) are beginning to be incorporated into practice but have not reached a degree of penetration to be meaningful from a macroscopic viewpoint.

What follows is an examination of general practice trends in the use of maintenance and induction therapy being applied to kidney, pancreas, kidney-pancreas, liver, intestine, heart, heart-lung, and lung transplant recipients. It is the most complete, detailed, and up-to-date analysis of its kind available. Importantly, it is only through the collective efforts of the transplant community that this information is made available to transplant professionals and the multiple constituents with an interest in the field.

KIDNEY TRANSPLANTATION

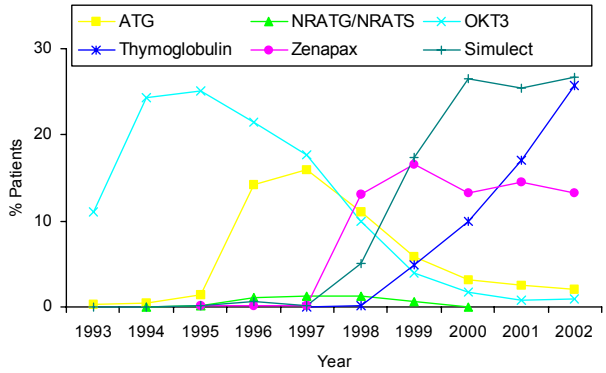
Trends in Induction Therapy in Kidney Transplantation

The period from 1993 to 2002 has seen a gradual but definitive shift toward routine use of antibody induction therapy. In 1993, 11% of patients undergoing kidney transplantation received antibody induction; by 2002, the proportion of kidney recipients who received antibody induction therapy was 65% *[Table 5.6a]*.

In addition to the increased use of antibody preparations for induction, there has been a marked shift in the type of antibody preparation (Figure IV-1). Muromonab-CD3 (OKT3®), which peaked in use in 1995 (administered to 25% of kidney transplant recipients) and accounted for virtually all the antibody used for induction, by 2002 had fallen to 1%. Similar trends were observed for equine antithymocyte globulin (ATGAM®). Equine antithymocyte globulin, which had peaked in use in 1997 (received by 16% of kidney transplant recipients),

by 2002 had fallen to 2%. The overwhelming majority of patients receiving antibody induction in 2002 received agents not available in 1993. These new agents included rabbit antithymocyte globulin (Thymoglobulin®), which accounted for 26% of patients, basiliximab (Simulect®), which accounted for 27%, and daclizumab (Zenapax®), which accounted for 13% of patients *[Table 5.6a]*. It is interesting to note that although daclizumab received FDA approval prior to basiliximab, basiliximab very quickly became the most commonly used induction agent shortly after its approval by the FDA. This may be related to the smaller number of doses (two) associated with its approved use and the ability to give both doses during the initial hospitalization at the time of transplantation.

Figure IV-1. Trends in Kidney Transplantation Induction Immunosuppression, 1993-2002



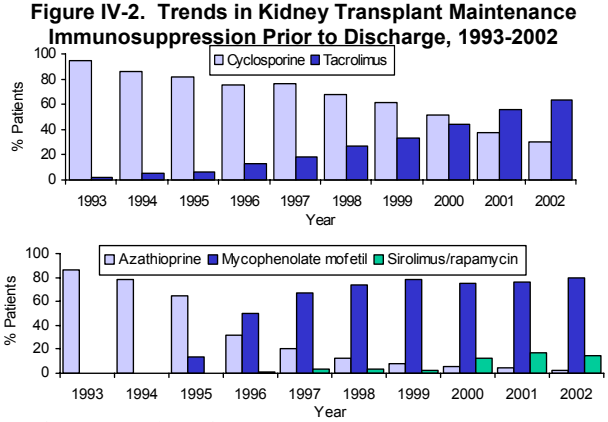
Source: *2003 OPTN/SRTR Annual Report,* Table 5.6a.

Induction therapy was used less frequently in recipients of kidneys from living versus deceased donors, but additional SRTR analysis showed that the difference was small. In 2002, the proportion of living and deceased donor recipients receiving induction therapy was 62% and 67%, respectively. With respect to the type of induction agent used in recipients of kidneys from deceased donors, rabbit antithymocyte globulin was used most commonly (29%), followed by basiliximab (27%). However, the type of induction agent used most commonly in recipients of kidneys from living donors was basiliximab (27%), followed by rabbit antithymocyte globulin (21%).

Trends in Maintenance Immunosuppression Therapy Prior to Discharge in Kidney Transplantation

Calcineurin inhibitors. In 1993, 95% of patients undergoing kidney transplantation received cyclosporine; only 2% received tacrolimus (the latter had not yet been approved by the FDA) (Figure IV-2). The trend over the next 10 years has been a gradual but inexorable decline in the use of cyclosporine, down to 30% in 2002. Most of the cyclosporine used has been Neoral®, 22%, and Gengraf®, 7%. Sandimmune® accounted for 1% and Eon® for 0.2%. Tacrolimus use has increased steadily as cyclosporine use has decreased (Figure IV-2). In 2002, tacrolimus was used in 63% of kidney transplant recipients *[Table 5.6b]*. The reasons for this conversion are most likely related to multicenter trial data that have suggested lower rates of acute rejection and lower rates of steroid-resistant rejection associated with tacrolimus (1,2). Cosmetic issues, i.e., the absence of hirsutism with tacrolimus, have also played a role.

Figure IV-2. Trends in Kidney Transplant Maintenance Immunosuppression Prior to Discharge, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 5.6b.

Antimetabolites and rapamycin. In 1993, azathioprine, the only routinely available antimetabolite, was used in 86% of kidney transplant recipients; by 2002, this had decreased to 2% (Figure IV-2). Mycophenolate mofetil, which was approved by the FDA in 1995, has seen its use increased to 79% of patients undergoing kidney transplantation. This high percentage rate has remained relatively constant over the last several years. In all, 81% of kidney recipients received some sort of antimetabolite in 2002. Rapamycin was received by 15% of the patients in 2002. This was down slightly from 17% in 2001 *[Table 5.6b]*. The most popular combination regimen in recent years has included tacrolimus and mycophenolate mofetil, which has been utilized in the majority of patients undergoing kidney (or pancreas) transplantation. This combination has been shown to be effective in several single and multicenter prospective randomized trials (2-4).

Corticosteroids. In 1993, 99% of patients received corticosteroids, either in the form of intravenous methylprednisone or prednisone. In 2002, 91% of patients received corticosteroids, suggesting that there is a growing percentage of patients who are receiving either steroid avoidance or near avoidance protocols after kidney transplantation (5-7) *[Table 5.6b]*.

Trends in Maintenance Immunosuppression Therapy for the First Year in Kidney Transplantation

Calcineurin inhibitors. The data in this section mirror the data described in the previous section. Cyclosporine was used in 96% of kidney transplant recipients in 1992. This had decreased to 39% by 2001. In 2001, Neoral® accounted for the vast majority of cyclosporine use (31%), Gengraf® accounted for 9%, Sandimmune® 3%, and Eon® 0.3%. Tacrolimus, which had not yet been approved in 1992, accounted for 3% of kidney transplant patients; by 2001, this figure had increased to 64%, probably for the reasons discussed above *[Table 5.6c]*.

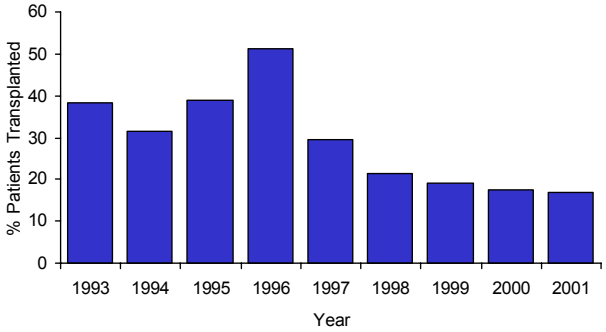
Antimetabolites and rapamycin. The use of antimetabolites remained high in 2001 at 83% in kidney transplant recipients; however, this was down somewhat from 1999, when it was 89%. Azathioprine usage decreased from 87% in 1992 to 6% in 2001, and mycophenolate mofetil increased from 1% in 1992 to 80% in 2001. Rapamycin use increased from 0% in 1992 to 21% in 2001; virtually all this increase has occurred since its FDA approval in 1998 *[Table 5.6c]*.

Corticosteroids. Corticosteroids again remain in use in virtually all patients undergoing kidney transplantation; this percentage has fallen very slightly from 99.5% in 1992 to 96% in 2001, suggesting that there is a small but growing percentage of patients who are no longer receiving corticosteroids *[Table 5.6c]*.

Trends in Anti-rejection Treatment in Kidney Transplantation

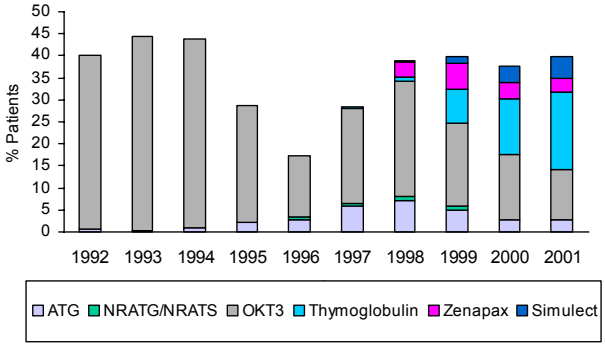
The first important observation to be made about anti-rejection treatment is that the need for it has decreased dramatically. In 1992, the percentage of kidney transplant recipients undergoing anti-rejection treatment was 38%; by 2001, it was 17% (Figure IV-3). In terms of therapies for rejection, the overwhelming majority of cases were treated with corticosteroids, and this percentage has changed slightly over the years, remaining at 81% in 1992 and in 2001. Antibody therapy use has decreased over the years, from 53% in 1992 to 37% in 2001. However, the specific antibodies used to treat rejection have changed dramatically (Figure IV-4). Antilymphocyte globulin (ALG), which peaked at 21% in 1993, has disappeared from practice *[Table 5.6d]*. Muromonab-CD3, which peaked at 44% in 1993, is now down to 11%. The use of rabbit antithymocyte globulin, which was 0% in 1993, is now up to 18%. Interestingly, in 2001, the interleukin-2 (IL-2) receptor antagonists daclizumab and basiliximab were used in 3% and 5% of patients, respectively, as anti-rejection therapy, although there are little data supporting their use *[Table 5.6d]*.

Figure IV-3. Trends in Incidence of Rejection at 1 Year in Kidney Transplant Recipients, 1993-2001



Source: *2003 OPTN/SRTR Annual Report,* Table 5.6d.

Figure IV-4. Trends in Antibody Therapy for Rejection Episodes Following Kidney Transplantation



Source: *2003 OPTN/SRTR Annual Report,* Table 5.6d.

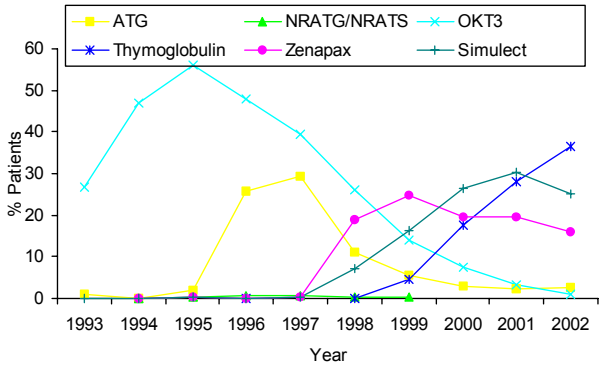
PANCREAS TRANSPLANTATION

Trends in Induction Therapy in Pancreas Transplantation

The use of induction therapy has been shown to significantly improve pancreas graft survival rates in several subgroups. According to data from the International Pancreas Transplant Registry, the use of induction therapy in simultaneous pancreas-kidney (SPK) transplant recipients with systemic venous-enteric exocrine drainage significantly improves pancreas graft survival rates (8,9). Interestingly, pancreas graft survival is not improved with induction therapy in the subgroups with portal venous-enteric or bladder drainage. Furthermore, SPK transplant recipients who receive induction therapy benefit from a reduced incidence and severity of biopsy-confirmed, treated, acute kidney rejection episodes. However, in recipients given anti-T-cell depleting induction agents, there was also a statistically significantly higher rate of CMV viremia/syndrome, especially in the subgroup of

recipients who received organs from CMV serologically positive donors (10). For the numerically smaller groups of solitary pancreas recipients (pancreas after kidney (PAK) and pancreas transplant alone (PTA)), the addition of induction therapy is associated with a clinically significant improvement in pancreas graft survival rates. In the PAK category, the 3-year actuarial pancreas graft survival with induction therapy is 74% versus 64% without. In the PTA category, the 1-year functional survival rate for recipients with induction therapy was 86% versus 74% without.

Figure IV-5. Trends in Simultaneous Kidney-Pancreas Transplantation Induction Immunosuppression, 1993-2002



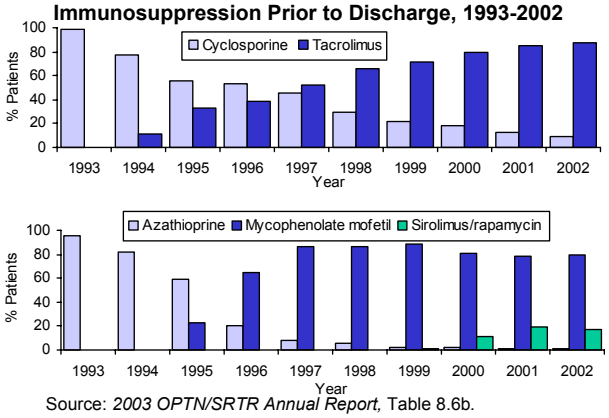
Source: *2003 OPTN/SRTR Annual Report,* Table 8.6a.

The use of antibody induction in pancreas transplant recipients has been relatively more common than in kidney transplantation. In SPK recipients, induction was used in 74% of patients in 2002. As in kidney transplantation, the specific agents have changed dramatically (Figure IV-5), so that while muromonab-CD3 was used in 56% of patients in 1995, use had decreased to 0.9% by 2002. Similarly, while equine antithymocyte globulin was used in 30% of cases undergoing SPK in 1997, use had decreased to 3% by 2002. Between 1993 and 2002, the use of rabbit antithymocyte globulin increased from 0% to 37%; the use of daclizumab increased from 0% to 16%; and the use of basiliximab increased from 0% to 25% *[Table 8.6a]*. In PAK and PTA patients, the same trends are observed. In PAK, no antibody induction was used in 1993, but in only 28% of cases in 2002 was antibody induction not used. Most of the antibody induction in 2002 was with rabbit antithymocyte globulin (51%), daclizumab (26%), and basiliximab (8%) *[Table 7.6a]*. Similarly, in PTA patients, antibody induction was not used in 33% of patients in 2002; 58% received rabbit antithymocyte globulin, 34% received daclizumab, and 5% received basiliximab *[Table 6.6a]*.

Trends in Maintenance Immunosuppression Therapy Prior to Discharge in Pancreas Transplantation

Calcineurin inhibitors. The decrease in the use of cyclosporine between 1993 and 2002 has been even more pronounced in kidney-pancreas transplants (Figure IV-6). In 1993, 98% of patients received cyclosporine; this was down to 9% in 2002, with 7% receiving Neoral®, 2% receiving Gengraf®, 0.7% receiving Sandimmune®, and 0.2% receiving Eon®. Tacrolimus usage increased to 87% of SPK recipients in 2002, up from 0% in 1993 *[Table 8.6b]*. Similar findings have been noted in both PAK and PTA patients; tacrolimus use has increased from 0% to 86% between 1993 and 2002 in PAK patients and from 10% to 95% in PTA patients *[Tables 6.6b, 7.6b]*.

Figure IV-6. Trends in SPK Transplant Maintenance Immunosuppression Prior to Discharge, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 8.6b.

Antimetabolites and rapamycin. As in kidney-pancreas transplants, antimetabolites continued to be used in the vast majority of patients, although this percentage decreased from 95% in 1993 to 80% in 2002 (Figure IV-6). Azathioprine usage fell from 95% to 0.9%, while mycophenolate mofetil has increased from 0% to 79%; this is down somewhat from 1999, where 88% of SPK patients received mycophenolate mofetil, and probably reflects the increased use of rapamycin. Rapamycin use in SPK patients increased from 0% in 1993 to as high as 20% in 2001; in 2002, it was down to 18% *[Table 8.6b]*. In PAK patients, the use of antimetabolites decreased from 100% to 74%. Azathioprine usage decreased from 100% to 0.3%. Mycophenolate mofetil use increased from 0% to 74%, but this represents a decrease from a peak of 92% in 1997. In PAK patients, the use of rapamycin increased from 0% to a peak of 21% in 2001, down to 19% in 2002 *[Table 7.6b]*. In PTA patients, antimetabolite usage decreased from 87% in 1993 to 66% in 2002 *[Table 6.6b]*. Azathioprine usage again virtually disappeared, decreasing from 87% to 1%, and

mycophenolate mofetil usage increased from 0% to 64%, the latter representing a decrease from 89% in 1997. In PTA patients, rapamycin usage increased steadily from 0% in 1993 to 16% in 2002.

Corticosteroids. Corticosteroids were used in 99% of patients undergoing SPK in 1993; this has decreased over the last couple of years to 87% in 2002, reflecting an increased use of steroid-free protocols (11). In PAK patients, the data from the early 1990s seem somewhat incomplete, but the percentages from 1997 and 1998, with 95% and 99% receiving steroids, decreased slightly to 89% by 2002. For PTA patients, the same trends were observed *[Tables 6.6b, 7.6b, 8.6b]*.

Trends in Maintenance Immunosuppression Therapy for the First Year in Pancreas Transplantation

Calcineurin inhibitors. The change in the use of calcineurin inhibitors has again been more marked in kidney-pancreas transplants. Cyclosporine use decreased from 99.8% to 16% between 1992 and 2001; most of this again was with Neoral®, 12%, Gengraf®, 3%, Sandimmune®, 2%, and Eon®, 0.4%. In SPK recipients, tacrolimus use from 0.5% in 1992 to 89% in 2001 *[Table 8.6c]*. The findings in PAK and PTA patients were even more dramatic. In PAK patients, cyclosporine use decreased from 100% in 1992 to 15% in 2001; tacrolimus use increased from 0% to 93%. In PTA patients, cyclosporine use decreased from 89% to 8% between 1992 and 2001, and tacrolimus use increased from 11% in 1992 to 99% in 2001 *[Tables 7.6c, 6.6c]*.

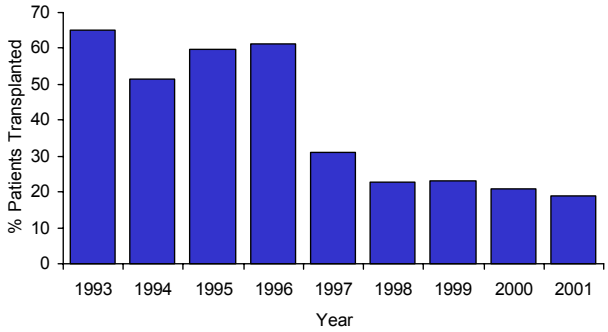
Antimetabolites and rapamycin. Antimetabolite use decreased from 99% in 1992 to 79% in 2001 in kidney-pancreas transplants. There was a shift from azathioprine, which decreased from 99% to 2% during this time period, to mycophenolate mofetil, which went up from 0% to 78%. The latter number is a decrease from 1998, where 92% of SPK patients received mycophenolate mofetil; it likely reflects the increasing use of rapamycin. In PAK and PTA patients, the same trends are present. There has been a steady increase in use of rapamycin in SPK patients, increasing from 0% to 27% between 1992 and 2001 *[Table 8.6c]*. This has been mirrored in PAK patients: rapamycin use has gone up from 0% to 29% *[Table 7.6c]*. In PTA patients, rapamycin use has increased from 0% to 15%. The latter, however, presents a decrease from 2000, where 25% of PTA patients received rapamycin *[Table 6.6c]*.

Corticosteroids. Corticosteroid use in SPK patients decreased slightly from 100% in 1992 to 92% in 2001, reflecting an increased use of steroid-weaning protocols (12,13). Steroid use, however, has remained relatively stable in PAK patients and almost as high in PTA patients *[Table 8.6c]*.

Trends in Anti-rejection Treatment in Pancreas Transplantation

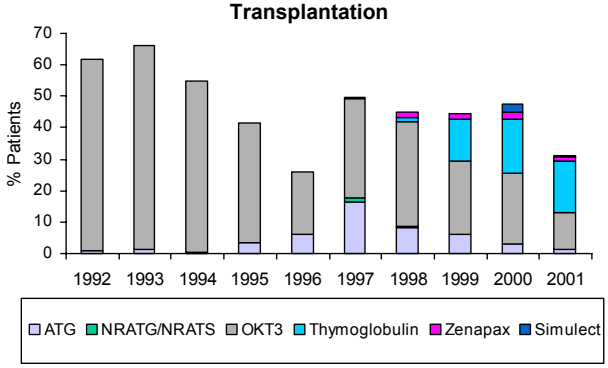
As in kidney transplantation, there has been a marked reduction in the need for anti-rejection therapy. From 1992 to 2001, the incidence of rejection in SPK patients declined from 66% to 19%, in PAK patients from 45% to 14%, and in PTA patients from 54% to 13% (Figure IV-7) *[Tables 8.6d, 7.6d, 6.6d]*. Antibody use decreased from 73% in 1992 to 29% in 2001 in SPK patients, and again the type of agents changed from muromonab-CD3 and equine antilymphoblast globulin (61% and 25%, respectively, in 1992), to rabbit antithymocyte globulin and muromonab-CD3, accounting for 17% and 12% of patients, respectively, in 2001 (Figure IV-8). Corticosteroid usage remained stable at just over 85% *[Table 8.6d]*. In PAK and PTA patients, antibody therapies were used in a somewhat higher percentage of patients by 2001 (63% in PAK patients, 62% in PTA patients) *[Tables 6.6d, 7.6d]*. The nature of these agents has also changed, as in the case of SPK.

Figure IV-7. Trends in Incidence of Rejection at 1 Year in Simultaneous Kidney-Pancreas Transplant Recipients, 1993-2001



Source: *2003 OPTN/SRTR Annual Report,* Table 8.6d.

Figure IV-8. Trends in Antibody Therapy for Rejection Episodes Following Simultaneous Kidney-Pancreas Transplantation



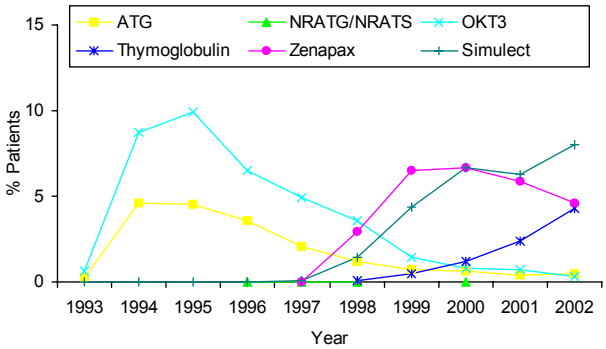
Source: *2003 OPTN/SRTR Annual Report,* Table 8.6d.

LIVER TRANSPLANTATION

Trends in Induction Therapy in Liver Transplantation

According to OPTN/SRTR data, between 1993 and 2001, the use of induction agents varied from 10% to 15% of recorded cases; by 2002, this figure had crept up to 18%. During the last 10 years, the induction agents of choice underwent gradual change. Earlier in the era, muromonab-CD3 was the predominant agent used, reaching a zenith in 1995 when 10% of recipients received it. Since then, the use of muromonab-CD3 has declined to almost nil, whereas the use of monoclonal anti-IL2 receptor agents has increased, so that by 2002, 13% of recipients received either daclizumab or basiliximab *[Table 9.6a]* (Figure IV-9). There also has been a modest resurgence in the use of rabbit antithymocyte globulin.

Figure IV-9. Trends in Liver Transplantation Induction Immunosuppression, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 9.6a.

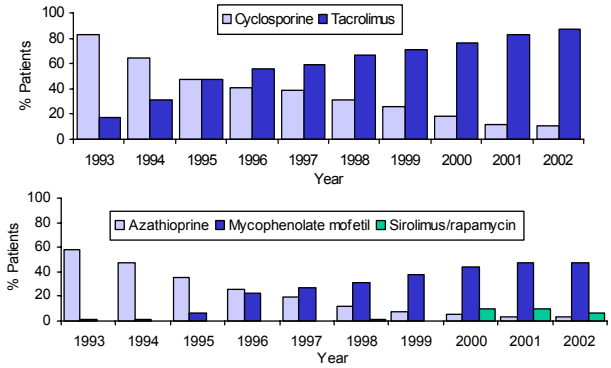
The reasons behind the gradual increased use of induction agents over the past five years are not clear. There are few studies to support or refute the use of anti-lymphocyte induction therapy in primary or repeated liver transplantation. One possible explanation is the introduction in 2002 of MELD-based allocation, in which liver transplantation candidates with renal failure receive priority; if such patients are being transplanted more quickly, it may reflect increased use of such agents as calcineurin inhibitor sparing agents in this population.

Trends in Maintenance Immunosuppression Therapy Prior to Discharge in Liver Transplantation

Serial data from 1993 through 2002 show some consistent patterns of immunosuppressant use prior to discharge. Throughout the period, liver allograft recipients were managed on multiple drug regimens based on corticosteroids and calcineurin inhibitors. Consistently, at least 50% of recipients received an antimetabolite. During the period for which data have been collected, there have been minor and inconsistent variances in the prevalence of corticosteroid use, so that 90% of recipients were discharged on corticosteroids in 2002, compared with 95% in 1993 or 88% in 1995 *[Table 9.6b]*.

Calcineurin inhibitors. In contrast, there have been striking shifts in drug selection among the calcineurin inhibitors and antimetabolites (Figure IV-10). For example, whereas cyclosporine (in any of its formulations) was administered to 83% of recipients prior to discharge in 1993, its rate of use declined every year since then to reach its current nadir of 10% in 2002. Whether the newly introduced practice of monitoring the blood level two hours (C2 monitoring) after ingestion rather than fasting trough levels will reverse this trend remains to be seen. The decline in use of cyclosporine has been mirrored by the increase in use of tacrolimus. Its use in immunosuppressant management prior to discharge increased every year from 1993 (18%) to 2002 (87%) *[Table 9.6b]*.

Figure IV-10. Trends in Liver Transplant Maintenance Immunosuppression Prior to Discharge, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 9.6b.

Antimetabolites and rapamycin. Similarly, azathioprine was the antimetabolite of choice in 1993, being administered to 58% of recipients. This rate of use declined annually until 2001, when it reached a nadir of 3%. In 2002, azathioprine use showed a modest increase to 4%. At the same time azathioprine declined, mycophenolate mofetil gained in use, from 0.6% in 1993 to 48% in 2002 (Figure IV-10). These data suggest, but do not prove, that mycophenolate mofetil has replaced azathioprine in circumstances where the managing physicians believe that an antimetabolite is required. Finally, there has been a small increase in the use of rapamycin in the early postoperative period. It was administered to 9% and 10% of recipients in 2000 and 2001, respectively. Curiously, this prevalence of use declined to 7% in 2002, perhaps on account of reported difficulties with early postoperative management, such

as wound healing and integrity of the vascular anastomoses *[Table 9.6b]*.

Trends in Maintenance Immunosuppression Therapy for the First Year in Liver Transplantation

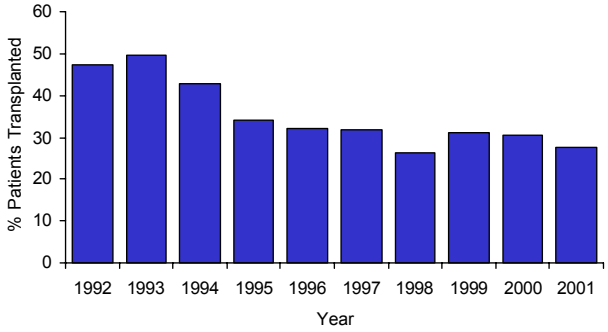
Perhaps the most surprising aspect of the OPTN/SRTR data on maintenance immunosuppression between discharge and the end of the first year is the unchanging results for use of corticosteroids. Thus, 93% of recipients in 1993 and 90% of recipients in 2001 received corticosteroids for their first postoperative year *[Table 9.6c]*. This is curious because of the widespread discussion of steroid reduction and withdrawal after liver transplantation (14-16). There are a number of possible explanations for this discrepancy. First, practice may have changed since 2001; if so, more contemporary data will show less use of corticosteroids. Second, there may be a gap between actual practice and what is advocated in publications, with practice not changing as much as anticipated. Third, the presented data do not consider the doses of corticosteroids in use, which may have been reduced over the past 10 years, albeit without withdrawal. Finally, the interval from discharge to the end of year one may be too brief, and data on maintenance up to year five might be more indicative of steroid withdrawal. In any case, the present data do not confirm a major shift away from the use of corticosteroids for maintenance immunosuppression in the first year after liver transplantation.

The data on calcineurin inhibitors and antimetabolites in the first year mirror the data reported prior to discharge, namely, 1) the widespread use of tacrolimus where previously cyclosporine was the favored calcineurin inhibitor and 2) the reduction in use of azathioprine and concomitant adoption of mycophenolate mofetil as the antimetabolite of choice. A small but significant percentage of patients also received rapamycin, the use of which grew from 0% in 1997 to 17% in 2001. These data do not address specifically the combinations in use. Nevertheless, judging by these data, even in 2001, more that 80% of liver transplant recipients were receiving at least two immunosuppressives (both corticosteroids and tacrolimus) and approximately half were receiving three *[Table 9.6c]*.

Trends in Anti-rejection Treatment in Liver Transplantation

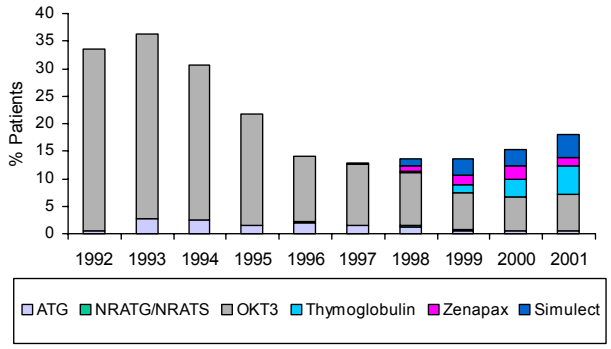
The proportion of liver transplant recipients treated for rejection has diminished over the 10-year time span, 1992 (47%) through 2001 (28%). However, during the most recent time period (1996 through 2001), the rate remained nearly constant (32% and 28%, respectively) (Figure IV-11). With respect to treatment therapies for rejection, the majority of cases were treated with corticosteroids. The percentage changed very little over the years: 94% in 1992 to 89% in 2001. Antibody therapy decreased slightly over the years, from 33% in 1992 to 17% in 2001. The nature of the antibodies used to treat rejection changed dramatically (Figure IV-12). Muromonab-CD3, which peaked at 34% in 1993, went down to 7% in 2001. Rabbit antithymocyte globulin, for which usage was 0% in 1993, was used in 5% of cases in 2001. Interestingly, the IL-2 receptor antagonists daclizumab and basiliximab were used in 2% and 4% of patients, respectively, as anti-rejection therapy in 2001, although there are little data supporting their use *[Table 9.6d]*.

Figure IV-11. Trends in Incidence of Rejection at 1 Year in Liver Transplant Recipients, 1992-2001



Source: *2003 OPTN/SRTR Annual Report,* Table 9.6d.

Figure IV-12. Trends in Antibody Therapy for Rejection Episodes Following Liver Transplantation



Source: *2003 OPTN/SRTR Annual Report,* Table 9.6d.

INTESTINAL TRANSPLANTATION

Trends in Induction Therapy in Intestinal Transplantation

The numbers of intestinal transplants remain small: 107 in 2002. The data presented do not distinguish between combined liver-small bowel transplantation and isolated

small bowel transplantation. In the past five years, induction chemotherapy has become more common. The prevalence has risen from 41% in 1998 to 57% in 2002. Rabbit antithymocyte globulin, basiliximab, and daclizumab were all used, without one agent establishing clinical predominance *[Table 10.6a]*.

Trends in Maintenance Immunosuppression Therapy Prior to Discharge in Intestinal Transplantation

Calcineurin inhibitors. Exclusive and almost universal use of tacrolimus (96% in 2002) has been the pattern prior to discharge throughout the period under review. Conversely, cyclosporine was used in no one. Up to year 2000, there was a similar, almost universal use of corticosteroids. However, in the two most recent years, corticosteroid use prior to discharge has declined to 80% and 64%, respectively *[Table 10.6b]*. These data are difficult to explain, especially since a similar decline was not observed in corticosteroid use in the first year after discharge (see below).

Antimetabolites and rapamycin. Rapamycin was used prior to discharge in 19% of intestinal transplant recipients in 2002. This frequency had declined from a peak of 39% in 2000. Given the small numbers, it is difficult to infer the reasons for such changes in practice. The use of antimetabolite agents has been similarly inconsistent, and, most recently, no recipients were recorded as receiving azathioprine and only 11% received mycophenolate mofetil *[Table 10.6b]*.

Trends in Maintenance Immunosuppression Therapy for the First Year in Intestinal Transplantation

The practice patterns for maintenance immunosuppression from discharge through the first year mirror those described above for transplant admission. Once again, tacrolimus was used in all recipients to the absolute exclusion of cyclosporine. This pattern has remained unchanged since 1996. Corticosteroids were also almost universal during this period, a pattern that has remained constant with minor variations since 1993 *[Table 10.6c]*.

The use of other agents is much less consistent over time. No clear trend regarding antimetabolites was discernable, with wide shifts from year to year. While recognizing the limited data, it appears that mycophenolate mofetil, which peaked at 57% in 1996, had fallen out of favor and was administered to only 3% of cases in 2001. Rapamycin was recorded in 1999, 2000, and 2001 only. The frequency of its use has fluctuated widely *[Table 10.6c]*.

Trends in Anti-rejection Treatment in Intestinal Transplantation

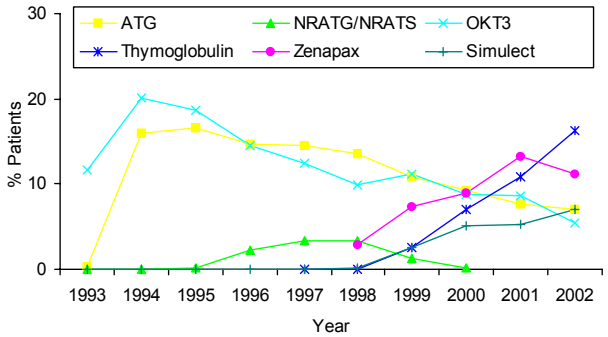
The proportion of intestine transplant recipients treated for rejection over the first posttransplant year has diminished over the 10-year time span, from 1992 (77%) through 2001 (36%). The data do not indicate the proportion of recipients with multiple rejection episodes. With respect to treatment therapies for rejection, virtually all recipients received corticosteroids as part of their anti-rejection therapy. Antibody therapy remained relatively constant: 48% in 1993 and 35% in 2001. The nature of the antibodies used to treat rejection has not changed appreciably. In 1993, all antibody therapy was muromonab-CD3. It is still the most commonly used antibody for treating rejection. Rabbit antithymocyte globulin was used in 8% of cases in 2001 *[Table 10.6d]*.

HEART TRANSPLATATION

Trends in Induction Therapy in Heart Transplantation

Trends for the use of induction therapy in heart transplantation have been similar to those seen in kidney transplantation; however, there appears to be a lag time of roughly two years. This likely represents the general reluctance of thoracic organ transplant physicians to try newer therapies until safety and efficacy have been established in other organ groups. In general, over the last decade, there has been an increase in the percentage of patients receiving induction therapy, from 12% in 1993 to 45% in 2002. This may be explained, in part, by the fact that a higher risk population (i.e., patients presenting with more diabetes, renal dysfunction, and older age) is now being transplanted than a decade ago. There have been several obvious trends for specific agents (Figure IV-13). The most frequently used induction agents have been muromonab-CD3 and equine antithymocyte globulin; however, their use has rapidly fallen off in the last several years to 5% and 7%,

Figure IV-13. Trends in Heart Transplantation Induction Immunosuppression, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 11.6a.

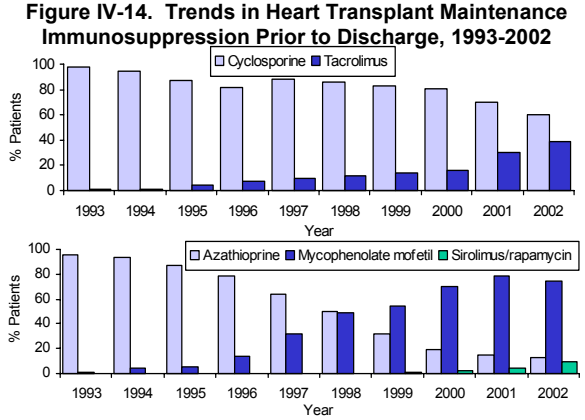
respectively. In contrast, the use of rabbit antithymocyte globulin has increased from 0% four years ago to 16% in 2002. Likewise, the use of anti-IL-2 receptor antibodies (daclizumab and basiliximab) has increased from 0% five years ago to 18% in 2002. The use of either rabbit antithymocyte globulin or an anti-IL-2 receptor antibody now appears to be the dominant strategy for induction in heart transplantation *[Table 11.6a]*.

Trends in Maintenance Immunosuppression Therapy Prior to Discharge in Heart Transplantation

From 1993 to 2002, there have been no major changes in the general scheme of immunosuppression therapy prior to discharge for heart transplant recipients. The basic therapeutic strategy for the majority of patients still includes a calcineurin inhibitor, an antimetabolite, and corticosteroids. However, there have been some fairly dramatic changes in agents within each class.

Calcineurin inhibitors. Calcineurin inhibitor use at the time of discharge remains essentially 100% (Figure IV-14). Cyclosporine remains the most frequently used calcineurin inhibitor, although its use has fallen from 98% in 1993 to 61% in 2002. Of those who received cyclosporine, approximately 46% received Neoral® and 13% received Gengraf® (a small percentage, 3%, received Sandimmune®). The use of tacrolimus has increased proportionally to the decrease in cyclosporine use. Tacrolimus is now used in 39% of heart transplant recipients at the time of discharge *[Table 11.6b]*.

Figure IV-14. Trends in Heart Transplant Maintenance Immunosuppression Prior to Discharge, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 11.6b.

Antimetabolites and rapamycin. The use of antimetabolites (azathioprine and mycophenolate mofetil) at the time of discharge has remained fairly constant over the past decade, ranging from 96% in 1993 to 84% in 2002 (Figure IV-14). Within this class of immunosuppressants, mycophenolate mofetil has assumed the dominant role over the past few years. In 2002, mycophenolate mofetil was used in 75% of heart transplant recipients at the time of discharge, while azathioprine use had fallen to 12%. A slight fall-off in antimetabolite use over the past few years is likely explained by the increasing use of rapamycin, now used in 10% of heart transplant recipients at the time of discharge. Other agents, such as cyclophosphamide, are rarely used in heart transplantation *[Table 11.6b]*.

Corticosteroids. Use of corticosteroids has fluctuated little in the past decade (a low of 94%, a high of 97%). In 2002, corticosteroids were used in 97% of heart transplant recipients at the time of discharge *[Table 11.6b]*.

Trends in Maintenance Immunosuppression Therapy for the First Year in Heart Transplantation

In 2001, the most common maintenance therapy combination for heart transplant recipients within the first year after transplantation consisted of corticosteroids, cyclosporine or tacrolimus, and mycophenolate mofetil *[Table 11.6c]*.

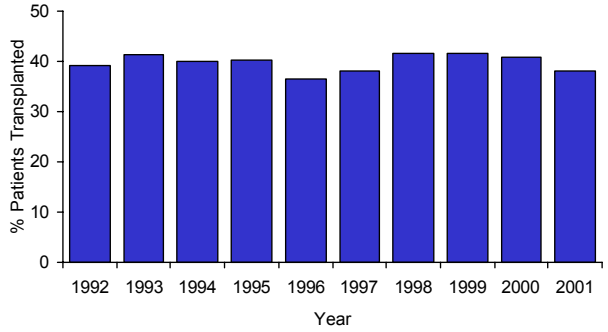
Calcineurin inhibitors. Therapy with cyclosporine or tacrolimus remains the cornerstone of maintenance immunosuppression in heart transplant recipients. Over the past 10 years, there has been a trend toward less use of cyclosporine and more use of tacrolimus. Cyclosporine use has decreased from 99% in 1992 to 65% in 2001, with Neoral® being the most frequent formulation. The use of tacrolimus has greatly increased from 1% to 43% during the same time interval *[Table 11.6c]*.

Antimetabolites and rapamycin. Although antimetabolites are still frequently used within the first year after heart transplantation, there has been a shift in practice over the last 10 years. The use of azathioprine dominated up until 1996 (97% in 1992, down to 15% in 2001). The use of mycophenolate mofetil now appears to be standard practice (81% in 2001) in heart transplantation. Overall, there appears to be a slight decline in the use of the standard antimetabolites as a class. In 1992, approximately 97% of heart transplant recipients received either azathioprine or mycophenolate mofetil. In 2001, the use of either azathioprine or mycophenolate mofetil fell to 95%. Concurrent with this trend, there was an increase in use of other novel immunosuppressant agents. In 2001, approximately 8% of heart transplant recipients received rapamycin within the first year after transplantation *[Table 11.6c]*.

Corticosteroids. The vast majority of heart transplant recipients are treated with corticosteroids as part of

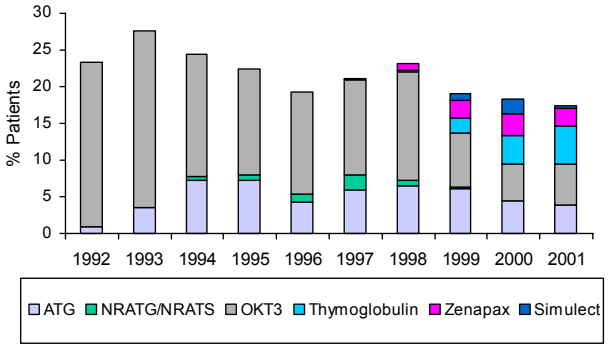
maintenance therapy during the first year after transplantation. Over the last 10 years, there has been no clear trend in the use of corticosteroids. In 2001, 91% of heart transplant recipients received either prednisone or methylprednisolone *[Table 11.6c]*.

Figure IV-15. Trends in Incidence of Rejection at 1 Year in Heart Transplant Recipients, 1992-2001



Source: *2003 OPTN/SRTR Annual Report,* Table 11.6d.

Figure IV-16. Trends in Antibody Therapy for Rejection Episodes Following Heart Transplantation



Source: *2003 OPTN/SRTR Annual Report,* Table 11.6d.

Trends in Anti-rejection Treatment in Heart Transplantation

In the last decade, it appears that the rates for treatment of rejection within the first year after heart transplantation have not changed (39% in 1992 and 38% in 2001) (Figure IV-15). For patients who require therapy for rejection, the use of corticosteroids has remained between 88% and 92%. During the last 10 years, the use of therapy with antibodies gradually decreased from 23% to 16%. When antibody therapy was used, muromonab-CD3 remained the most frequently used preparation, although its use has declined. In 1993, muromonab-CD3 was used in 24% of cases of rejection, whereas in 2001 it was used in only 6%. The use of equine antithymocyte globulin varied from 1% in 1992 to 7% in 1995, although the use of this agent may be declining (4% in 2001). The use of rabbit antithymocyte globulin has been steadily increasing over the past several years to 5% in 2001. The use of anti-IL-2 receptor antibodies for the treatment of rejection had increased to approximately 3% in 2001 *[Table 11.6d]*.

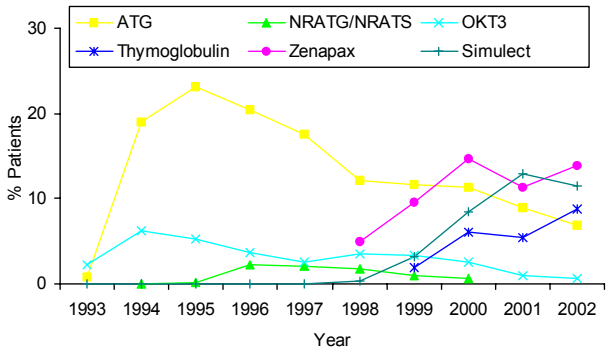
In summary, the treatment of rejection within the first year after heart transplantation remains based on corticosteroids, with a gradual decline in the use of antibody therapy noted over the past several years. When antibody therapy is used, there appears to be no consensus as to the specific preparation (Figure IV-16).

LUNG TRANSPLANTATION

Trends in Induction Therapy in Lung Transplantation

The trends for the use of induction therapy in lung transplantation have been similar to those seen in heart transplantation, with a general decrease seen in the use of muromonab-CD3 and equine antithymocyte globulin, and a concurrent increase in the use of rabbit antithymocyte globulin and anti-IL-2 receptor antibodies (daclizumab and basiliximab) (Figure IV-17). In general, over the last 10 years, there has been a gradual increase in the percentage of patients receiving induction therapy, from 3% in 1993 to 41% in 2002. There have been several obvious trends for specific agents. The most frequently used induction agent over the last 10 years was equine antithymocyte globulin, peaking in 1995 at 23%; however, in 2002, it was only reported in 7% of lung transplant recipients. The use of muromonab-CD3 peaked in 1994 at 6% but has now fallen to less than 0.6% in lung transplantation. In contrast, the use of rabbit antithymocyte globulin has increased from 0% four years ago to 9% in 2002.

Figure IV-17. Trends in Lung Transplantation Induction Immunosuppression, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 12.6a.

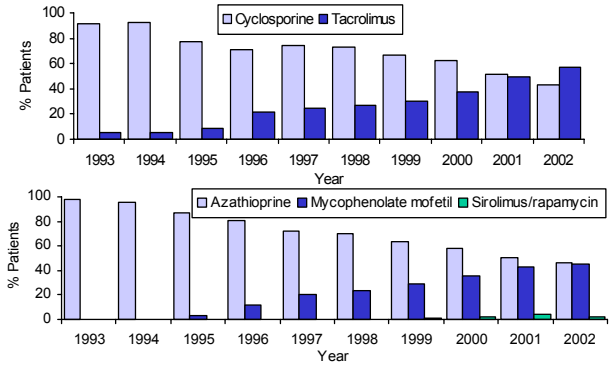
Likewise, the use of anti-IL-2 receptor antibodies (daclizumab and basiliximab) has increased from 0% six years ago to 25% in 2002. The use of either rabbit antithymocyte globulin or an anti-IL-2 receptor antibody now appears to be the dominant strategy for induction in lung transplantation *[Table 12.6a]*.

Trends in Maintenance Immunosuppression Therapy Prior to Discharge in Lung Transplantation

As in heart transplantation, from 1993 to 2002, there have been no major changes in the general scheme of immunosuppression therapy prior to discharge for lung transplant recipients. However, within the certain specific classes of immunosuppressants, there have been dramatic shifts in practice *[Table 12.6b]*.

Calcineurin inhibitors. Calcineurin inhibitor use at the time of discharge remains essentially 100%. Cyclosporine is no longer the most frequently used calcineurin inhibitor. Cyclosporine fell from 91% in 1993 to 43% in 2002. Of those who received cyclosporine, most received Neoral®. A small proportion received either Gengraf® or Sandimmune®. In contrast, the use of tacrolimus increased substantially. Tacrolimus is now used in 57% of lung transplant recipients at the time of discharge (Figure IV-18) *[Table 12.6b]*.

Figure IV-18. Trends in Lung Transplant Maintenance Immunosuppression Prior to Discharge, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 12.6b.

Antimetabolites and rapamycin. The use of antimetabolites (azathioprine and mycophenolate mofetil) at the time of discharge has remained fairly constant over the past 10 years, ranging from 98% in 1993 to 90% in 2002. Although the use of azathioprine has declined, and the use of mycophenolate mofetil has proportionally risen, this has not occurred to the same extent as is seen in heart transplantation. In 2002, azathioprine was used in 46% of lung transplant recipients at the time of discharge and mycophenolate mofetil was used in 45% (Figure IV-18). The use of rapamycin has not, as of yet, played much of a role in lung transplantation. Peak use in 2001 was only 4%. In 2002, rapamycin was only used in 2% of lung transplant recipients at the time of discharge. Other agents, such as cyclophosphamide, were rarely used in lung transplantation *[Table 12.6b]*.

Corticosteroids. Use of corticosteroids fluctuated little in the past decade (a low of 97% and a high of 99%). In 2002 corticosteroids were used in 99% of lung transplant recipients at the time of discharge *[Table 12.6b]*.

Trends in Maintenance Immunosuppression Therapy for the First Year in Lung Transplantation

In 2001, the most common maintenance therapy combination for lung transplant recipients within the first year after transplantation consisted of corticosteroids, tacrolimus, and either azathioprine or mycophenolate mofetil *[Table 12.6c]*.

Calcineurin inhibitors. As in heart transplantation, cyclosporine or tacrolimus remain the cornerstone of maintenance immunosuppression in lung transplant recipients. In the past decade, there was a trend toward less use of cyclosporine and more use of tacrolimus, to the point where tacrolimus now appears to be the agent of choice. Cyclosporine use has decreased from 93% in 1992 to 46% in 2001, with Neoral® being the most frequent formulation. The use of tacrolimus has increased from 7% to 69% during the same time interval *[Table 12.6c]*.

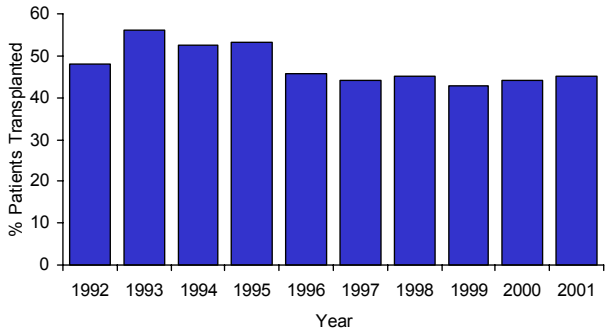
Antimetabolites and rapamycin. Although antimetabolites are still frequently used within the first year after lung transplantation, there was a shift in practice over the last decade. The use of azathioprine declined from 97% in 1992 to 49% in 2001. The use of mycophenolate mofetil concurrently increased from 0% to 52% over the same time period. Overall, there appeared to be a slight decline in the use of standard antimetabolites as a class. In 1992, approximately 97% of lung transplant recipients received azathioprine. In 2001, the use of either azathioprine or mycophenolate mofetil fell to 91%. Concurrent with this trend, there was an increase in use of other novel immunosuppressant agents. In 2001, approximately 11% of lung transplant recipients received rapamycin within the first year after transplantation *[Table 12.6c]*. However, the recent trend shows a decrease in use, perhaps related to the observation that airway anastomotic dehiscence is associated with use of rapamycin immediately after lung transplantation (17).

Corticosteroids. The vast majority of lung transplant recipients are treated with corticosteroids as part of maintenance therapy during the first year after transplantation. Within the last decade, there has been no clear trend in the use of corticosteroids. In 2001, nearly 100% of lung transplant recipients received either prednisone or methylprednisolone *[Table 12.6c]*.

Trends in Anti-rejection Treatment in Lung Transplantation

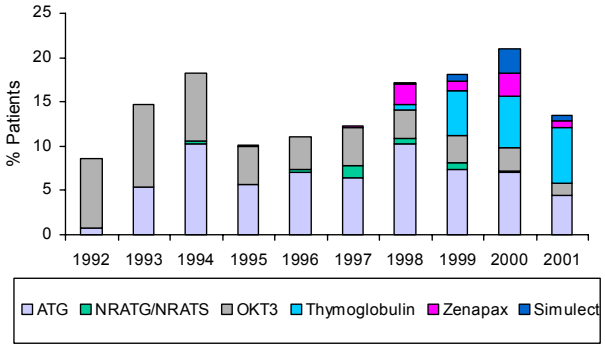
In the last decade, it appears that the rates for treatment of rejection within the first year after lung transplantation did not change substantially (48% in 1992 and 45% in 2001) (Figure IV-19). For patients who required therapy for rejection, the use of corticosteroids has remained between 88% and 97% *[Table 12.6d]*.

Figure IV-19. Trends in Incidence of Rejection at 1 Year in Lung Transplant Recipients, 1992-2001



Source: *2003 OPTN/SRTR Annual Report,* Table 12.6d.

Figure IV-20. Trends in Antibody Therapy for Rejection Episodes Following Lung Transplantation, 1992-2001



Source: *2003 OPTN/SRTR Annual Report,* Table 12.6d.

During the last 10 years, the use of therapy with antibodies ranged from 9% to 18%, with no clear trend. When antibody therapy was used, equine antithymocyte globulin was the most frequently used preparation, although its use declined from 10% in 1994 to 4% in 2001. The use of muromonab-CD3 declined from 10% in 1993 to 2% in 2001. The use of rabbit antithymocyte globulin has steadily increased over the past several years to 6% in 2001. The use of anti-IL-2 receptor antibodies for the treatment of rejection was approximately 1% in 2001 *[Table 12.6d]*.

In summary, the treatment of rejection within the first year after lung transplantation remains based on corticosteroids. The use of antibody therapy gradually increased between 1995 (10%) and 2000 (18%). However, its usage decreased in 2001 (12%). When antibody therapy is used, there appears to be no consensus as to the specific preparation (Figure IV-20) *[Table 12.6d]*.

HEART-LUNG TRANSPLANTATION

Trends in Induction Therapy in Heart-Lung Transplantation

The trends for the use of induction therapy in heart-lung transplantation have been somewhat erratic. The reason for this is that the overall number of en-bloc heart-lung transplants has decreased from a peak of 71 transplants in 1994 to as low as 27 in 2001 (32 in 2002). Thus, inference as to trends in such small numbers is difficult. In general, over the last decade there has been a gradual increase in the percentage of patients receiving induction therapy, from 12% in 1993 to 59% in 2002. However, the changes in practice appear to be somewhat random. The use of equine antithymocyte globulin peaked in 1995 at 44% and declined to 16% in 2002. The use of muromonab-CD3 remained relatively stable (6% in 2002). The use of rabbit antithymocyte globulin increased from 0% four years ago to a peak in 2001 at 12% (3% in 2002). The use of anti-IL-2 receptor antibodies (daclizumab and basiliximab) increased from 0% five years ago to 34% in 2002. The use of either equine antithymocyte globulin or an anti-IL-2 receptor antibody appears to be the dominant strategy for induction in heart-lung transplantation *[Table 13.6a]*.

Trends in Maintenance Immunosuppression Therapy Prior to Discharge in Heart-Lung Transplantation

As in heart transplantation, from 1993 to 2002 there have been no major changes in the general scheme of immunosuppression therapy prior to discharge for heart-lung transplant recipients. Shifts within the certain specific classes of immunosuppressants have not been as dramatic as seen with other organ types *[Table 13.6b]*.

Calcineurin inhibitors. Calcineurin inhibitor use at the time of discharge remains essentially 100%. Cyclosporine use has fallen from a high of 93% in 1994 to 62% in 2002. Of those who received cyclosporine,

most received Neoral®. A small proportion received either Sandimmune® or Gengraf®. In contrast, the use of tacrolimus increased substantially. Tacrolimus is now used in 43% of heart-lung transplant recipients at the time of discharge *[Table 13.6b]*.

Antimetabolites and rapamycin. The use of antimetabolites (azathioprine and mycophenolate mofetil) at the time of discharge remained fairly constant over the past 10 years, ranging from 94% in 1993 to 95% in 2002. Although the use of azathioprine has declined and the use of mycophenolate mofetil has proportionally risen, this has not occurred to the same extent as is seen in heart transplantation. In 2002, azathioprine was used in 52% of heart-lung transplant recipients at the time of discharge and mycophenolate mofetil was used in 48%. The use of other agents such as rapamycin has not occurred in heart-lung transplant patients at the time of discharge *[Table 13.6b]*.

Corticosteroids. The use of corticosteroids has fluctuated a little in the past decade (a low of 88% in 1996, a high of 100% in 1999-2002) *[Table 13.6b]*.

Trends in Maintenance Immunosuppression Therapy for the First Year in Heart-Lung Transplantation

Calcineurin inhibitors. Cyclosporine or tacrolimus remain the cornerstone of maintenance immunosuppression in heart-lung transplant recipients. Over the past 10 years, there has been a trend toward less use of cyclosporine and more use of tacrolimus. Cyclosporine use has decreased from 81% in 1992 to 50% in 2001, with Neoral® being the most frequent formulation. During the same time interval, the use of tacrolimus has increased greatly, from 19% to 75% *[Table 13.6c]*.

Antimetabolites and rapamycin. Although antimetabolites are still used frequently within the first year after heart-lung transplantation, there was a shift in practice over the last decade. The use of azathioprine declined from 97% in 1992 to 50% in 2001. Concurrently, the use of mycophenolate mofetil rose to 60%. The use of rapamycin increased to 10% in 2000; however, no first year heart-lung patients received rapamycin in 2001 *[Table 13.6c]*.

Corticosteroids. The vast majority of heart-lung transplant recipients were treated with corticosteroids as part of maintenance therapy during the first year after transplantation. In 2001, 95% of heart-lung transplant recipients received either prednisone or methylprednisolone *[Table 13.6c]*.

In 2001, the most common maintenance therapy combination for the small numbers of heart-lung transplant recipients within the first year after transplantation consisted of corticosteroids, tacrolimus, and mycophenolate mofetil *[Table 13.6c]*.

Trends in Anti-rejection Treatment in Heart-Lung Transplantation

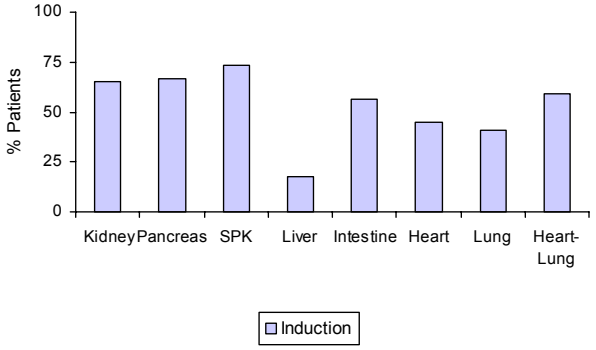
For first-year transplant recipients who require therapy for rejection, the use of corticosteroids has remained between 80% and 100% in the small number of patients who have received heart-lung transplants. During the last 10 years, the use of therapy with antibodies varied from 10% to 20%. When antibody therapy was used, muromonab-CD3, equine antithymocyte globulin, rabbit antithymocyte globulin and anti-IL-2 receptor antibodies were all used with no clear trends, given the small numbers of transplanted patients *[Table 13.6d]*.

COMPARISON OF ORGANS

Trends in Induction Therapy

The proportion of patients receiving induction therapy varied widely among organs (Figure IV-21). The highest use of induction therapy was reported for SPK and PAK transplants. Its use was reported in over 70% of the recipients in 2002; this was followed by PTA (67%), kidney (65%), intestine (57%), and thoracic (over 40%). Induction was not very common in liver transplants and was reported in only 18% of recipients in 2002 *[Tables 5.6a, 6.6a, 7.6a, 8.6a, 9.6a, 10.6a, 11.6a, 12.6a, 13.6]*.

Figure IV-21. Comparative Use of Immunosuppression for Induction Prior to Discharge, All Organs, 2002



Source: *2003 OPTN/SRTR Annual Report,* Table 5.6-13.6.

In the earlier years, muromonab-CD3 was the predominant induction agent used in most organs, except in thoracic transplantation, where the use of equine antithymocyte globulin was as common. A switch from equine antithymocyte globulin or muromonab-CD3 as the primary induction agent to IL-2

receptor antagonists (basiliximab and daclizumab) occurred in either 1998 or 1999 for kidney, kidney-pancreas, pancreas, liver, and intestine, followed by a switch from IL-2 receptor antagonists to rabbit antithymocyte globulin in 2000 or 2001. In 2002, rabbit antithymocyte globulin was used more often than IL-2 receptor antagonists for pancreas, kidney-pancreas, and intestine, whereas IL-2 receptor antagonists were used more commonly than rabbit antithymocyte globulin for liver and kidney transplants *[Tables 5.6a, 6.6a, 7.6a, 8.6a, 9.6a, 10.6a, 11.6a, 12.6a, 13.6a]*.

Both muromonab-CD3 and equine antithymocyte globulin were reported as common induction agents for thoracic organs in the earlier years and were replaced by IL-2 receptor antagonists in 2000 for lung and in 2001 for heart and heart-lung. While a switch to rabbit antithymocyte globulin occurred in 2002 for heart, IL-2 receptor antagonists remained the more common induction agent for lung and heart-lung in 2002 *[Tables 11.6a, 12.6a, 13.6a]*.

Trends in Maintenance Immunosuppression Therapy Prior to Discharge

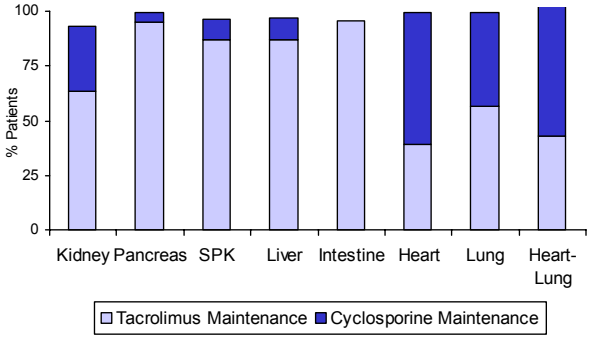
Immunosuppressive regimens used for maintenance therapy at discharge varied by organ (Figures IV-22 and IV-23). The use of corticosteroids as discharge maintenance immunosuppression was reported in the majority of transplant recipients. Corticosteroids were used in over 87% of recipients of kidney, SPK, PAK, and thoracic transplants, and in over 70% of recipients of PTA. The use of corticosteroids in intestine transplants was reported in over 80% of recipients until 2002, where the use was reported in only 64% of recipients *[Tables 5.6b, 6.6b, 7.6b, 8.6b, 10.6b, 11.6b, 12.6b, 13.6b]*.

Cyclosporine was the most-used calcineurin inhibitor in most organs until the introduction of tacrolimus around 1994. A switch from cyclosporine to tacrolimus occurred in 1995 for pancreas, in 1996 for liver, in 1997 for SPK, and in 2001 for kidney. Cyclosporine remained the calcineurin inhibitor agent of choice for heart and heart-lung through 2002, whereas a switch to tacrolimus was noted for lung in 2002. For intestine, tacrolimus has been the predominant calcineurin inhibitor agent since 1994. In 2002, the proportion of recipients reported with tacrolimus as discharge maintenance immunosuppression was 63% for kidney, 95% for PTA, 86% for PAK, 87% for SPK, 87% for liver, 96% for intestine, 39% for heart, 57% for lung, and 43% for heart-lung *[Tables 5.6b, 6.6b, 7.6b, 8.6b, 9.6, 10.6b, 11.6b, 12.6b, 13.6b]*.

Azathioprine was the favored antimetabolite agent for most organs until the introduction of mycophenolate mofetil in late 1995. A switch from azathioprine to mycophenolate mofetil occurred in 1996 for kidney, pancreas, SPK, and intestine; in 1997 for liver; and in 1999 for heart. Azathioprine remained the antimetabolite agent of choice for lung and heart-lung transplants. In 2002, the proportion of recipients reported with mycophenolate mofetil as discharge maintenance immunosuppression was 79% for kidney, 64% for PTA, 74% for PAK, 79% for SPK, 48% for liver, 11% for intestine, 75% for heart, 45% for lung, and 48% for heart-lung *[Tables 5.6b, 6.6b, 7.6b, 8.6b, 9.6b, 10.6b, 11.6b, 12.6b, 13.6b]*.

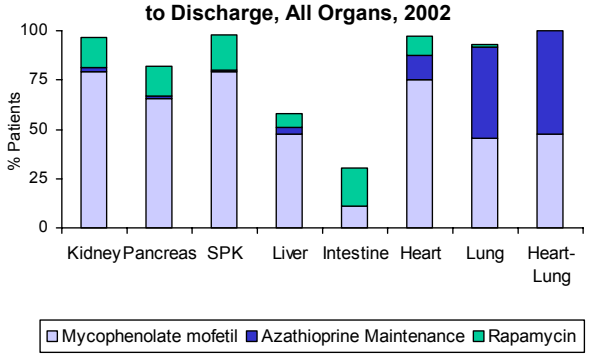
The use of rapamycin started to emerge in 2000 for all organs except heart-lung. In 2002, the use of rapamycin ranged from 15% to 20% in kidney, pancreas, SPK, and intestine transplants. During the same year, rapamycin was reported in 7% of liver, 10% of heart, and only 2% of lung transplant recipients *[Tables 5.6b, 6.6b, 7.6b, 8.6b, 9.6b, 10.6b, 11.6b, 12.6b]*.

Figure IV-22. Comparative Calcineurin Inhibitor Use for Immunosuppression Prior to Discharge, All Organs, 2002



Source: *2003 OPTN/SRTR Annual Report,* Table 5.6-13.6.

Figure IV-23. Comparative Use of Antimetabolite Maintenance and Rapamycin Immunosuppression Prior to Discharge, All Organs, 2002



Source: *2003 OPTN/SRTR Annual Report,* Table 5.6-13.6.

Trends in Maintenance Immunosuppression Therapy Between Discharge and One Year Posttransplant

The use of corticosteroids between discharge and one year after transplant was reported in the majority of transplant recipients. For transplants performed in 2001, the proportion of recipients with corticosteroids between discharge and one year ranged from 86% for intestine to 100% for lung *[Tables 5.6c, 6.6c, 7.6c, 8.6c, 9.6c, 10.6c, 11.6c, 12.6c, 13.6c]*.

Cyclosporine was the most reported maintenance calcineurin inhibitor between discharge and one year posttransplant in most organs until about 1994. A switch from cyclosporine to tacrolimus occurred for transplants performed in 1994 for PTA, in 1995 for liver, in 1996 for PAK, in 1997 for SPK, in 2000 for lung, and in 2001 for kidney and heart-lung. For heart, cyclosporine remained the calcineurin inhibitor agent of choice, whereas for intestine, tacrolimus has been the predominant calcineurin inhibitor agent since 1994. For transplants performed in 2001, the proportion of recipients reported with tacrolimus as maintenance immunosuppression between discharge and one year was 64% for kidney, 99% for PTA, 93% for PAK, 89% for SPK and liver, 100% for intestine, 43% for heart, 69% for lung, and 75% for heart-lung *[Tables 5.6c, 6.6c, 7.6c, 8.6c, 9.6c, 10.6c, 11.6c, 12.6c, 13.6c]*.

A switch from azathioprine to mycophenolate mofetil occurred for transplants performed in 1995 for PTA; in 1996 for kidney, PAK, SPK, liver, and intestine; in 1997 for heart; in 2001 for lung; and in 2000 for heart-lung. Although a switch from azathioprine to mycophenolate mofetil had occurred for intestinal transplants performed since 1996, azathioprine became the antimetabolite agent of choice again for transplants done in 2001. For lung, azathioprine remained the antimetabolite agent of choice, though it was used at a comparable rate compared with mycophenolate mofetil for transplants done in 2001 (50% vs. 52%). For transplants performed in 2001, the proportion of recipients reported with mycophenolate mofetil between discharge and one year was 80% for kidney, 75% for PTA, 79% for PAK, 78% for SPK, 50% for liver, 81% for heart, 52% for lung, 60% for heart-lung, and only 3% for intestine *[Tables 5.6c, 6.6c, 7.6c, 8.6c, 9.6c, 10.6c, 11.6c, 12.6c, 13.6c]*.

For most organs, the use of rapamycin between discharge and one year posttransplant started to emerge for transplants done in 1999 or 2000. For transplants performed in 2001, the use of rapamycin between discharge and one year ranged from 0% for heart-lung to 29% for PAK transplants *[Tables 5.6c, 6.6c, 7.6c, 8.6c, 9.6c, 10.6c, 11.6c, 12.6c, 13.6c]*.

Trends in Anti-rejection Treatment between Discharge and One Year Posttransplant

Although the proportion of recipients reported with antibody treatment for rejection may have fluctuated over the years, overall, there was a decreasing trend in its use between transplant and one year posttransplant for most organs. For transplants done in 1994, for example, 53% of kidney, over 60% of SPK and pancreas, about 30% of liver and intestine, and over 17% of thoracic transplants were reported with nonsteroid anti-rejection therapy between discharge and one-year posttransplant. In contrast, in 2002, 37% of kidney, 62% of PTA, 63% of PAK, 30% of SPK, 17% of liver, 16% of heart, 12% of lung, and 0% of heart-lung transplants were reported with noncorticosteroid anti-rejection therapy between discharge and one year posttransplant. Interestingly, the proportion of intestinal transplants treated for rejection remained at 35% *[Tables 5.6d, 6.6d, 7.6d, 8.6d, 9.6d, 10.6d, 11.6d, 12.6d, 13.6d]*.

The use of corticosteroids for anti-rejection therapy was more common than use of an antibody agent for most organs. Corticosteroids were the most common treatment for rejection between discharge and one year for transplants done in 2001 for at least 80% of kidney, PAK, SPK, liver, and intestine recipients. Over 90% of PTA, heart, lung, and heart-lung transplants performed in 2001 were reported with corticosteroids *[Tables 5.6d, 6.6d, 8.6d, 9.6d, 10.6d, 11.6d, 12.6d, 13.6d]*.

For most organs, muromonab-CD3 was the most common antibody therapy used to treat rejection between discharge and one year posttransplant during the earlier years. For transplants done in 2001, the proportion of recipients reported with muromonab-CD3 was 11% for kidney, 29% for PTA, 28% for PAK, 12% for SPK, 33% for intestine, and less than 10% for liver, heart, and lung transplants. ALG was also used in most organs except liver and intestine until about 1994, when it was replaced by equine antithymocyte globulin. The use of equine antithymocyte globulin as an anti-rejection agent was more common in thoracic transplants during the more recent years and was comparable with the use of muromonab-CD3 *[Tables 5.6d, 6.6d, 7.6d, 8.6d, 9.6d, 10.6d, 11.6d, 12.6d, 13.6d]*.

The use of rabbit antithymocyte globulin as an anti-rejection therapy started to be reported for transplants performed in 1999 for most organs. For transplants performed in 2001, the proportion of recipients reported with rabbit antithymocyte globulin rejection therapy between discharge and one year posttransplant was 18% for kidney, 17% for SPK, 38% for PTA, 35% for PAK, 5% for liver and heart, 8% for intestine, and 6% for lung *[Tables 5.6d, 6.6d, 7.6d, 8.6d, 9.6d, 10.6d, 11.6d, 12.6d]*.

SUMMARY

This review has documented marked changes in the use of immunosuppressive agents in solid organ transplantation over the past decade. Several consistencies have emerged with respect to the use of maintenance immunosuppression. There has been a transition within the calcineurin inhibitor era from the dominant use of cyclosporine to tacrolimus and the near ubiquitous use of mycophenolate mofetil over azathioprine. Chronic use of corticosteroids remains a mainstream practice despite increased attention to successful steroid sparing strategies. Induction therapy is being incorporated into immunosuppression protocols with increasing frequency. The agents employed are mostly IL-2 receptor antagonists, but clear trends indicate that T-cell depletion is being used more often. The result of these changes in clinical practice seems to indicate that the short-term outcomes have improved based on the observation that rates of rejection within the first year posttransplant have diminished (18). Future surveys of trends in immunosuppression use are unlikely to show a great deal of change over the next few years, but subtle signs of immunosuppression minimization (diminished use of steroids) and new induction therapies (e.g., Campath®) are likely to surface. Ultimately, one would like to know how today's choices of immunosuppression will affect outcomes in the long term. Future reports will be able to answer those questions.

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