# Azathioprine vs cyclosporine in recipients of HLA-identical renal allografts

INDERBIR S. GILL, MD; ERNEST E. HODGE, MD; ANDREW C. NOVICK, MD; STEVAN B. STREEM, MD; WILLIAM E. BRAUN, MD; LATA PARANANDI, MSHP

■ **BACKGROUND** Siblings with identical human leukocyte antigens (HLA) are preferred transplant donors.

■ **OBJECTIVE** To compare the outcomes in azathioprine-treated and cyclosporine-treated recipients of renal transplants from HLA-identical siblings.

■ **METHODS** Retrospective review.

■ **RESULTS** From August 1980 to June 1989, 53 consecutive patients received renal transplants from HLA-identical donors. These patients received prednisone and either azathioprine (n = 26) or cyclosporine (n = 27). A mean of 8.4 years elapsed since transplantation in the azathioprine-treated patients and 4.7 years elapsed in the cyclosporine-treated patients. The 5-year patient and graft survival rates were 100% and 92%, respectively, for azathioprine-treated patients and 96% and 83%, respectively, for cyclosporine-treated patients ($P = .379$ for comparison of graft survival). There was no difference between the two groups in the number of rejections or the time to the first rejection episode. At 5 years after transplantation, cyclosporine-treated patients had a significantly higher median serum creatinine concentration (1.7 mg/dL) than did azathioprine-treated patients (1.3 mg/dL, $P = .018$). Maintenance steroid therapy was successfully withdrawn in six azathioprine-treated patients and seven cyclosporine-treated patients.

■ **CONCLUSIONS** Azathioprine and cyclosporine produce equally satisfactory outcomes in this immunologically favored group. The need for continued steroid therapy in these patients requires further study.

■ INDEX TERMS: AZATHIOPRINE; CYCLOSPORINE; KIDNEY TRANSPLANTATION; FOLLOW-UP STUDIES ■ CLEVE CLIN J MED 1994; 61:206–210

From the Departments of Urology (I.S.G., E.E.H., A.C.N., S.B.S.), Nephrology and Hypertension (W.E.B.), and Biostatistics and Epidemiology (L.P.), The Cleveland Clinic Foundation.

Address reprint requests to A.C.N., Department of Urology, A100, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

SIBLINGS WITH identical human leukocyte antigens (HLA) constitute an immunologically privileged group. Patients who receive renal transplants from HLA-identical siblings survive longer than recipients of kidneys from partially matched living-related or cadaver donors, and their grafts last longer.[1,2] In spite of the relatively weak immunogenicity between HLA-identical siblings, the recipients require immunosuppressive therapy because unidentified antigenic differences can cause rejection.[3] Nevertheless, because of the high success rate achieved in HLA-identical renal transplantation, some authorities suggest that less-intense immunosuppressive therapy would cause fewer complications than standard regimens and still maintain good allograft function.[4,5] The issue of optimal immunosuppression in these patients is currently unresolved. This study compares and evaluates the relative merits and efficacy of azathioprine- and cyclosporine-based immunosuppressive regimens in HLA-identical living-related renal transplantation.

## MATERIALS AND METHODS

From August 1980 to June 1989, 53 consecutive patients (35 men and 18 women) received kidneys from HLA-identical siblings at The Cleveland Clinic Foundation. The HLA-identical status of the donor-recipient pairs was determined by serologic HLA typing and by direct mixed-lymphocyte culture techniques. Matching at the D locus was confirmed by a low stimulatory index with one- and two-way mixed-lymphocyte culture.[6] Forty-six recipients were white, four were black, and three were Asian. Their ages ranged from 16 to 60 years (mean 33 years).

The cause of end-stage renal disease was glomerulonephritis in 17 patients, diabetic glomerulosclerosis in nine, pyelonephritis in six, nephrosclerosis in four, renal hypoplasia in three, adult polycystic kidney disease in three, lupus nephritis in two, Alport's syndrome, Goodpasture's syndrome, obstructive uropathy, and drug-induced nephropathy in one each, and unknown in five. Before transplantation, 11 patients underwent native bilateral nephrectomy and four patients underwent splenectomy. There were 50 primary transplantations and three repeat transplantations.

There were two distinct maintenance immunosuppressive regimens. Twenty-six patients received azathioprine and prednisone, and 27 patients received cyclosporine and prednisone. Azathioprine (2 to 3 mg/kg/day) was begun 36 hours before transplantation, and subsequent dosages were adjusted according to the white blood cell count. Cyclosporine (14 to 17 mg/kg/day) was begun 36 hours before transplantation and tapered to 12 to 14 mg/kg/day at 2 weeks and 10 mg/kg/day at 4 weeks. The subsequent dosage of cyclosporine was adjusted to maintain trough whole-blood levels (determined by high-performance liquid chromatography) from 150 to 300 ng/mL at 0 to 1 month, 100 to 200 ng/mL at 1 to 6 months, 50 to 150 ng/mL at 6 to 12 months, and less than 100 ng/mL thereafter. Prednisone was given immediately after transplantation in both groups at a dosage of 2 mg/kg/day up to 120 mg/day and was tapered thereafter to 30 mg/day at 1 month, 20 mg/day at 2 months, and approximately 0.1 mg/kg/day at 6 months after transplantation.

All patients received 1 g of methylprednisolone intravenously at the time of surgery. Episodes of rejection were diagnosed using clinical, biochemical, and radiologic data, and the majority were confirmed by percutaneous needle biopsy of the transplant. Episodes of rejection were treated with methylprednisolone (125 mg intravenously every 6 hours for 3 days), antilymphocyte globulin (10 to 20 mg/kg/day for 10 to 14 days), muromonab-CD3 (5 mg intravenously for 10 to 14 days), an increased dosage of oral prednisone, or a combination of these treatments. Serum creatinine concentrations were recorded before, after, and at the peak of episodes of rejection.

**TABLE 1**
CHARACTERISTICS OF PATIENTS
WHO RECEIVED AZATHIOPRINE OR CYCLOSPORINE

| Number | Azathioprine (n = 26) | Cyclosporine (n = 27) |
|---|---|---|
| Men | 18 | 17 |
| Women | 8 | 10 |
| White patients | 24 | 22 |
| Other races | 2 | 5 |
| Patients older than age 50* | 2 | 2 |
| Primary transplantations | 24 | 26 |
| Repeat transplantations | 2 | 1 |
| Patients with diabetes | 4 | 5 |
| Nephrectomies before transplantation | 7 | 4 |
| Splenectomies before transplantation | 2 | 2 |
| Median blood transfusions before transplantation (interquartile range) | 4(6) | 2(4)† |

*The average age in the azathioprine group was 32.8 years; in the cyclosporine group, 33.7 years
†$P = .01$ by Wilcoxon rank-sum test

Whenever cyclosporine or azathioprine produced a toxic reaction or when a rejection episode occurred, either "crossover" or triple therapy was initiated. Triple therapy consisted of maintenance immunosuppression with azathioprine, cyclosporine, and prednisone. If kidney function improved after cyclosporine was reduced in dosage or stopped, we assumed that cyclosporine had been causing the reduction in kidney function and considered this an episode of cyclosporine-induced nephrotoxicity. An attempt was made to discontinue maintenance prednisone in all compliant patients commencing 6 months after transplantation; this was accomplished in six azathioprine-treated patients and in seven cyclosporine-treated patients who continued azathioprine or cyclosporine monotherapy thereafter.

Baseline data were similar in patients who received azathioprine and in those who received cyclosporine (*Table 1*). There were no significant differences in age, sex, original diagnoses, race, number

**TABLE 2**
MEDIAN SERUM CREATININE CONCENTRATIONS (MG/DL)
AFTER RENAL TRANSPLANTATION IN PATIENTS RECEIVING AZATHIOPRINE OR CYCLOSPORINE

| Years after transplantation | Azathioprine group n | Azathioprine group Median serum creatinine concentration, mg/dL | Azathioprine group Interquartile range | Cyclosporine group n | Cyclosporine group Median serum creatinine concentration, mg/dL | Cyclosporine group Interquartile range | *P* value |
|---|---|---|---|---|---|---|---|
| 1 | 26 | 1.4 | 0.3 | 23 | 1.4 | 0.8 | .26 |
| 2 | 26 | 1.3 | 0.4 | 24 | 1.7 | 0.5 | .008 |
| 3 | 26 | 1.3 | 0.6 | 21 | 1.6 | 0.6 | .1 |
| 4 | 19 | 1.3 | 0.6 | 18 | 1.5 | 0.4 | .052 |
| 5 | 23 | 1.3 | 0.5 | 12 | 1.7 | 0.6 | .018 |

of nephrectomies and splenectomies before transplantation, and number of repeat transplantations between the groups. However, the median number of third-party blood transfusions before transplantation was four in azathioprine-treated patients and two in cyclosporine-treated patients ($P = .01$). Complete follow-up data were obtained for all patients in this study. The interval since transplantation ranged from 4.9 to 11.7 years (mean 8.3 years) in azathioprine-treated patients and from 1 to 7.3 years (mean 4.7 years) in cyclosporine-treated patients.

In the analysis of results from this study, we considered allograft loss or patient death with a functioning graft as allograft failure. We estimated patient and graft survival by the Kaplan-Meir method[7] and used the log-rank test for group survival comparisons.[8]

## RESULTS

There was no significant difference in patient or graft survival between the two groups. Patient survival at 5 years was 100% in azathioprine-treated patients and 96% in cyclosporine-treated patients. One cyclosporine-treated patient died of acute cardiopulmonary arrest following seizure activity 5 months after transplantation. She had experienced no episodes of rejection and had a well-functioning graft at the time of death. Graft survival at 1, 2, 3, and 5 years was 100%, 100%, 100%, and 92%, respectively, for azathioprine-treated patients and 92%, 88%, 88%, and 83%, respectively, for cyclosporine-treated patients ($P = .379$). One or more episodes of rejection occurred in nine azathioprine-treated patients (35%) and in eight cyclosporine-treated patients (30%) ($P = .7$). Six azathioprine-treated patients had one episode of rejection and three patients had two episodes; of the cyclosporine-treated patients, six had one episode of rejection and two had three episodes. There was no significant difference between the treatment groups in either the duration between transplantation and the first episode of rejection or in the number of patients who experienced episodes of rejection within the first 3 months after transplantation.

The only significant difference at baseline between the treatment groups was in the number of third-party transfusions before transplantation. In order to assess the effect of blood transfusions on graft survival and on time to rejection, we used a stratified log-rank test to compare the treatment groups while controlling for this variable. This analysis showed no significant difference between treatment groups with respect to graft survival or time to first rejection.

The median serum creatinine concentrations after transplantation are shown in *Table 2*. The median serum creatinine concentrations were not significantly different between the treatment groups at 1 year. However, at 2 and 5 years, the mean serum creatinine concentrations were significantly lower in azathioprine-treated patients than in cyclosporine-treated patients, and the difference was marginally significant at 4 years.

Currently, six patients (23%) continue to take azathioprine as monotherapy and seven (26%) take cyclosporine as monotherapy. These patients were completely weaned from prednisone at 6 to 47 months (mean 20.6 months) after transplantation. Patient and allograft survival is 100% in this subgroup of 13 patients. No episodes of rejection occurred in these patients following discontinuation of prednisone.

One patient who began with azathioprine therapy crossed over to cyclosporine therapy because of

rejection. Two patients who started with cyclosporine therapy crossed over to azathioprine therapy because of cyclosporine-induced nephrotoxicity. Five patients receiving cyclosporine began triple therapy because of problems with rejection or cyclosporine-induced nephrotoxicity. All of these patients continued to maintain good allograft function following crossover or triple therapy.

## DISCUSSION

After identical twins, HLA-identical siblings represent the most immunologically favored donor-recipient group for renal transplantation. Various reports have documented 2-year patient and graft survival rates ranging between 88% and 96%.[2,9,10] Some studies have implied a beneficial effect of cyclosporine in these patients compared with conventional immunosuppression with azathioprine.[11] Suggested advantages of cyclosporine therapy have included better graft survival, fewer rejection episodes, fewer blood transfusions before transplantation, and, possibly, reduced need for steroids. Disadvantages of cyclosporine include a possible adverse effect on long-term graft function, a higher cost, and possible increased risks of vascular complications and hypertension.[12,13] Because of the excellent prognosis of HLA-identical renal transplant recipients, some authors have suggested that using less-intense immunosuppressive therapy would diminish associated side effects and still maintain excellent graft survival.[4,5,11,14–16]

We undertook the present study to compare the effects of two immunosuppressive regimens (azathioprine and prednisone, or cyclosporine and prednisone) on outcome in HLA-identical live-donor renal transplantation. There was no significant difference in the 5-year patient or graft survival rates between these two groups. However, the small sample size gives our study only a low power to detect these differences. To ensure a statistical power of 80%, a sample size of 242 patients (121 patients in each group) would be needed.

There was no difference in the number of rejections or in the time to the first rejection episode between these groups. Patients treated with azathioprine had received more blood transfusions before transplantation, but a stratified log-rank test showed that this did not influence graft survival or time to rejection. Patients treated with cyclosporine had significantly higher median serum creatinine concentrations at 5 years after transplantation ($P = .018$) than did patients treated with azathioprine.

Our results show equivalent graft survival with cyclosporine or azathioprine in HLA-identical recipients up to 5 years after transplantation. This is similar to the findings of Morris,[17] who reported excellent graft survival with azathioprine and prednisone in HLA-identical live-donor recipients, with most patients ultimately weaned from prednisone.[17] However, Flechner[11] reported that cyclosporine was superior to azathioprine in this setting. In the latter study, graft survival at 4.5 years after transplantation was significantly better in patients treated with cyclosporine (96%) than with azathioprine (79%); the serum creatinine levels were somewhat lower in the azathioprine group but the difference was not statistically significant.

In a multicenter study from the Southeastern Organ Procurement Foundation, HLA-identical live-donor recipients who received cyclosporine had worse renal function at 1 year after transplantation than patients who received azathioprine; graft survival was equivalent.[13] Patients receiving cyclosporine spent more time in the hospital and underwent more transplant biopsies for episodes of graft dysfunction. Our patients who received cyclosporine also had diminished renal function at 5 years after transplantation. However, the overall mean serum creatinine level in these patients remains satisfactory, and the long-term significance of this finding is therefore not clear.

Although steroids form an integral part of most immunosuppressive protocols, they cause serious side effects, eg, progressive atherosclerotic vascular disease, hypertension, hyperlipidemia, hyperglycemia, infection, avascular necrosis of bone, and cushingoid appearance. Several authors have suggested that steroids may be safely withdrawn in HLA-identical living-related transplant recipients. In a series of 49 HLA-identical recipients, MacDonald[4] described 12 patients receiving cyclosporine monotherapy who had 3-year patient and allograft survival rates of 100% and 96%, respectively. In a series of 66 HLA-identical recipients, Hariharan[5] described 39 patients undergoing azathioprine monotherapy. Nine of these patients had to resume prednisone for a variety of reasons. In the remaining patients, prednisone was withdrawn with no rejection episodes or graft losses. In our series, six HLA-identical recipients received maintenance therapy with azathioprine alone, and seven recipients re-

ceived maintenance therapy with cyclosporine alone; there were no episodes of rejection or graft losses in these patients. Evidently, both azathioprine and cyclosporine monotherapy can confer adequate immunosuppression for at least some HLA-identical allograft recipients.

In summary, we have reviewed the long-term outcome of renal transplantation in 53 HLA-identical live-donor recipients who received either azathioprine or cyclosporine. Our results show equally satisfactory graft and patient survival rates with either regimen. The long-term use of cyclosporine is associated with mild impairment of renal function compared with azathioprine. The need for continued maintenance steroid therapy in these patients requires further study.

## REFERENCES


1. **Simmons RL, Van Hook EJ, Yunis EJ, et al.** 100 Sibling kidney transplants followed 2 to 7-1/2 years: a multifactorial analysis. Ann Surg 1977; **185:**196–204.
2. **Cheigh JS, Chami J, Stenzel KH, et al.** Renal transplantation between HLA-identical siblings—comparison with transplant from HLA semi-identical related donors. N Engl J Med 1977; **296:**1030–1034.
3. **Seigler HF, Ward FE, McCoy RE, Weinrerth JL, Gunnels JC, Strickel DL.** Long-term results with forty five living related renal allograft recipients genotypically identical for HLA. Surgery 1977; **81:**274–283.
4. **MacDonald AS, Belitsky P, Bitter-Suermann H, Cohen A.** Cyclosporine as primary therapy for A-matched living related donor kidney graft recipients. Transplant Proc 1989; **21:**1667–1669.
5. **Hariharan S, First MR, Munda R, et al.** Prednisone withdrawal in HLA-identical living related donor transplant recipients. Transplant Proc 1989; **21:**1617–1619.
6. **Mickelson EM, Hansen JA.** The mixed lymphocyte culture (MLC) reaction: a standard assay for direct (one-way) MLC testing and for HLA-D typing. In: Zachary AA, Braun WE, editors. American Association of Clinical Histocompatibility Testing Laboratory Manual. New York: American Association of Clinical Histocompatibility Testing, 1981:IV-2-1–IV-2-38.
7. **Kaplan EL, Meier P.** Nonparametric estimation from incomplete estimations. J Am Stat Assoc 1958; **53:**457–481.
8. **Lee ET.** Statistical methods for survival data analysis. New York: John Wiley and Sons, 1992:104–128.
9. **Ascher NL, Simmons RL, Noreen H, et al.** 100 HLA-identical sibling transplants. Prognostic factors other than histocompatibility. Ann Surg 1979; **189:**209–216.
10. **Flechner SM, Kerman RH, Van Buren CT, Epps L, Kahan BD.** The use of cyclosporine in living-related renal transplantation. Donor-specific hyporesponsiveness and steroid withdrawal. Transplantation 1984; **38:**685–691.
11. **Flechner SM, Kerman RH, Van Buren CT, et al.** Does cyclosporine improve the results of HLA-identical renal transplantation? Transplant Proc 1987; **19:**1485–1488.
12. **Curtis JJ, Luke RG, Dubovsky E, Diethelm AG, Whelchel JD, Jones P.** Cyclosporine in therapeutic doses increases renal allograft vascular resistance. Lancet 1986; **2:**477–479.
13. **Sanfilippo F, Vaughan WK.** Results in live-donor renal transplantation: The SEOPF multicenter study. Transplant Proc 1987; 19:1489–1491.
14. **First MR, Munda R, Kant KS.** Steroid withdrawal following HLA-identical related donor transplantation. Transplant Proc 1981; **13:**319–322.
15. **Iwasaki Y, Ozaki A, Furao K.** Withdrawal of immunosuppressive drugs after renal transplantation: a world survey. Transplant Proc 1982; **14:**225–230.
16. **Steinman TI, Zimmerman CE, Monaco AP, et al.** Steroids can be stopped in kidney transplant recipients. Transplant Proc 1981; **13:**323–327.
17. **Morris PJ.** Cyclosporine. In: Morris PJ, editor. Kidney transplantation: principles and practice. 3rd ed. Philadelphia: Saunders, 1988:285–317.


**CME CREDIT**

*To earn CME Category I credit, see test on p. 240*