

# Long-Term Results of a Randomized Study Comparing Three Immunosuppressive Schedules with Cyclosporine in Cadaveric Kidney Transplantation

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**Abstract.** In this randomized controlled trial started in October 1990, 354 cadaveric kidney transplant recipients were assigned to receive either cyclosporine (CsA) monotherapy (115 patients), CsA + steroids (117 patients), or CsA + steroids + azathioprine (122 patients). The median follow-up was 85.1 mo. Thirty-one deaths occurred (infection, 12; cardiovascular disease, 11; neoplasia, 4; and others, 4), and 65 grafts were lost, mostly due to acute (15) or chronic rejection (50). The cumulative graft half-life was 18.1 yr. According to the "intention-to-treat," the 9-yr actuarial patient and graft survival were 94.0% and 73.3%, respectively, in monotherapy, 87.3% and 65.9% in dual therapy, and 87% and 72.2% in triple therapy ( $P = 0.647$ ). At the last follow-up, the percentage of patients who remained with the original treatment was 51.2% in monotherapy, 81.7% in dual therapy, and 63.3% in triple

therapy. At the seventh year, the mean creatinine clearances were  $54.9 \pm 17.6$  ml/min in monotherapy,  $57.9 \pm 23.4$  in dual therapy, and  $60.6 \pm 20.7$  in triple therapy ( $P = 0.375$ ). Cataracts ( $P = 0.000$ ), osteoporosis ( $P = 0.000$ ), and cardiovascular complications ( $P = 0.000$ ) were more frequent in dual or triple therapy than in monotherapy. Actuarial graft survival at 9 yr in patients on monotherapy who had to have steroids added was similar to that of the other two groups (62.2% versus 69.3%,  $P = 0.134$ ). In conclusion, actuarial patient and graft survivals did not differ among the three schemes. The long-term renal function and survival were not affected in the patients on monotherapy who needed the addition of steroids. Monotherapy was associated with a lower incidence of extra-renal complications than the other two regimens.

In 1997 we reported the results of a multicenter randomized trial in cadaveric renal transplant recipients treated with either cyclosporine (CsA) alone, or in combination with steroids, or in combination with steroids and azathioprine (1). No significant differences were observed in the 4-yr graft survival, but patients assigned to steroid-free immunosuppression showed a lower incidence of cardiovascular, osteoskeletal, and ocular complications. To evaluate the results in the long-term of these different regimens and to verify whether the avoidance of

steroids did or did not expose the patients to the risk of late allograft dysfunction, we updated the results of this trial at 9 yr.

## Materials and Methods

### Patients

The study started on October 1990, and enrollment was closed on April 1993. Patients aged 16 to 70 yr who received a first or second cadaveric donor kidney were considered for the study. Patients with more than 50% preformed cytotoxic antibodies (36 patients), those who developed an acute rejection within the first 5 d after transplantation (35 patients), or those who still needed dialysis at the fifth posttransplant day (122 patients) were excluded from the study (total number of excluded patients, 193). In total, 354 cadaver renal transplant recipients were recruited. At posttransplant day 5, after informed consent was obtained, patients were randomly assigned to receive either CsA alone (monotherapy), CsA + steroids (dual therapy), or CsA + steroids + azathioprine (triple therapy), according to a randomization list balanced per center.

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## Therapies

**Peritransplant Therapy (Days 0 to 5).** Patients were given 5 mg/kg of CsA intravenously at transplantation and in the first post-transplant day. Oral CsA (Sandimmune®, Sandoz Pharma Ltd., Basel, Switzerland) was given at a dose of 12 mg/kg per d, divided into two administrations every 12 h. Intravenous methylprednisolone (MP) was given at a dose of 500 mg at transplantation, followed by 200 mg on day 1 and 50 mg on day 2. MP was then administered orally in a single morning dose of 16 mg/d.

**CsA Alone (Monotherapy).** MP was stopped at the fifth post-transplant day. CsA was reduced to 10 mg/kg per d on day 15 and was then gradually tapered by 2 mg/kg every 2 wk to a maintenance dose of 4 to 5 mg/kg per d and further reduced after the first year. Adjustments were made to keep CsA whole blood trough levels, as assessed by a specific monoclonal antibody, between 175 and 400 ng/ml in the first 3 mo after transplantation, between 125 and 300 ng/ml from 3 to 6 mo, between 100 and 225 ng/ml until the twelfth month, and between 75 and 200 ng/ml thereafter. Patients on monotherapy who had more than one acute rejection were switched to either dual or triple therapy.

**CsA + Steroids (Dual Therapy).** CsA dosage and blood levels were the same as for monotherapy. Oral MP was kept at 16 mg/d for 3 mo and then was gradually tapered to 8 mg/d by the end of the sixth month.

**CsA + Steroids + Azathioprine (Triple Therapy).** The CsA dose was reduced to 10 mg/kg per d on day 6 and to 8 mg/kg per d 1 wk later. It was then tapered by 2 mg/kg per d every 2 wk to a maintenance dose of 3 mg/kg per d. CsA blood levels were kept between 100 and 200 ng/ml by the end of the second month and between 50 and 150 ng/ml thereafter. As in the dual therapy regimen, oral MP was reduced to 8 mg/d at the end of month 6. From day 6, azathioprine was given at a dose of 1.5 mg/kg per d for 3 mo and then tapered to a maintenance dose of 1 mg/kg per d. If the leukocyte count fell below 3000/mm<sup>3</sup>, azathioprine was temporarily stopped until leukocytes rose to 5000/mm<sup>3</sup>.

**Definitions.** Acute rejection was diagnosed whenever there was an increase in serum creatinine of at least 30% above previous values, not justified by other complications. Ultrasonography was performed routinely to exclude other causes of graft failure. Renal biopsy was performed in doubtful cases.

Chronic allograft dysfunction was defined as a progressive worsening of renal function not explained by urological or vascular complications, CsA toxicity, or recurrence of original renal disease. The diagnosis was confirmed in all patients either by renal biopsy or by histologic assessment on the removed kidney that showed interstitial fibrosis with tubular atrophy associated with obliterative endoarteriopathy due to myofibroblast proliferation, with focal disruption of the elastica and/or signs of chronic transplant glomerulopathy.

## Statistical Analyses

All the analyses were performed according to the intention-to-treat principle. For this study, data were updated at 9 yr (up to December 31, 1999) for 328 of the 354 originally randomized patients, and for the remaining 26 patients data were available up to December 1997; these patients were considered as censored after that date. Patient and graft survival were evaluated by the Kaplan and Meier product limit estimate. Treatment groups were compared by the log rank test. Pure graft survival was also calculated, censoring death for patients who died with a functioning kidney. The creatinine clearance was estimated by the Cockcroft and Gault formula (2). The results were

multiplied by 0.85 for women. ANOVA was used to analyze laboratory parameters and cyclosporine doses. The general linear model was used for the analysis of time variations of creatinine clearances. The relative frequency of adverse events in the different treatment groups, put together according to an arbitrary classification, was compared by the Cochran-Mantel-Henszel test over the distribution of patients with/without any event in the class. Graft half-life was calculated according to the method of Cho and Terasaki (3).

## Results

The mean follow-up for the whole population was 73.4 ± 28.8 mo (95% CI, 70.4 to 76.4). The median follow-up was 85.1 mo. Thirty-one deaths occurred (Table 1). About half of them (14 deaths, 13 with a functioning kidney) occurred after the fourth year. Of note, four of the six deaths in the monotherapy group occurred in patients to whom steroids had been added to the therapy. There was only one cardiovascular death in monotherapy *versus* 10 in the other two groups. The overall 9-yr actuarial patient survival was 89.2%. It was about 94.0% for monotherapy, 87.3% for dual therapy, and 87.0% for triple therapy (log rank,  $P = 0.261$ ) (Figure 1).

Sixty-five grafts were lost, mostly because of chronic allograft nephropathy (Table 2). The overall 9-yr actuarial graft survival was 70.6%. The cumulative graft half-life was 18.1 yr. At the last follow-up visit, 84 of the 115 patients (73%) originally randomized to monotherapy, 82 of the 117 patients (70%) assigned to dual therapy, and 90 (73.8%) of the 122 assigned to triple therapy group had a functioning kidney. The 9-yr actuarial graft survival, according to the intention-to-treat principle, was 73.3% for monotherapy, 66% for dual therapy, and 72.2% for triple therapy (log rank,  $P = 0.647$ ) (Figure 2). The graft half-life was 18.4 yr for patients on monotherapy, 15.3 yr for patients on dual therapy, and 21.1 yr for patients on triple therapy. The pure graft survival at 9 yr was 74.7% for monotherapy, 77.2% for dual therapy, and 82.3% for triple (log rank,  $P = 0.574$ ).

Of the monotherapy group, 80 patients had at least one episode of acute rejection (69.5%) *versus* 58 (49.5%) patients on dual and 60 (49.2%) on triple therapy ( $\chi^2 P < 0.01$ ). At the end of the follow-up, 43 (51.2%) of 84 of the patients in the monotherapy group were still in the originally randomized scheme, 67 (81.7%) of 82 were still under the scheduled dual therapy regimen, and 57 (63.3%) of 90 were still in the original triple therapy. Many treatment shifts were made in the first

*Table 1.* Causes of death in 31 patients assigned to receive CsA alone (mono), CsA + steroids (dual), or CsA + steroids + azathioprine (triple)

Cause	Mono	Dual	Triple
Cardiovascular	1	6	4
Infections	3	5	2
Neoplasia	2	1	4
Liver failure	—	1	1
Guillain-Barré	—	—	1
Total ( $n = 31$ )	6	13	12

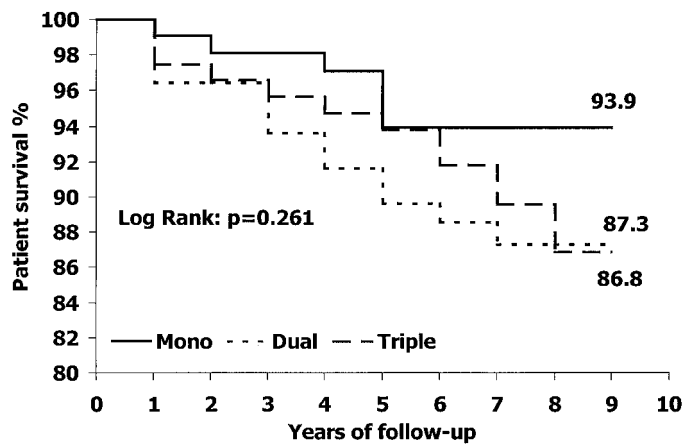


Figure 1. Actuarial patient survival according to the three different immunosuppressive schemes at randomization (intention-to-treat analysis).

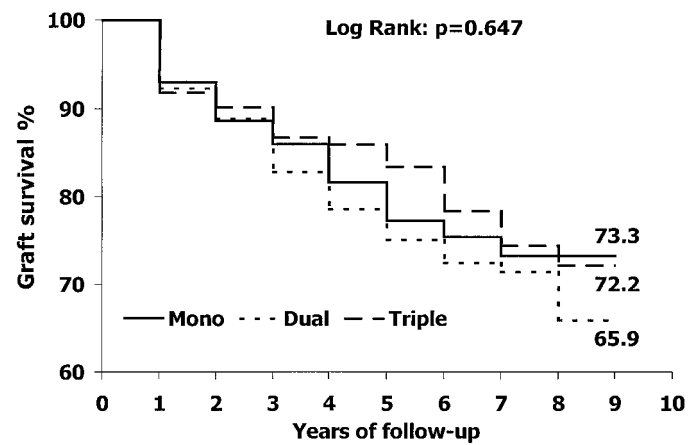


Figure 2. Actuarial graft survival according to the three different immunosuppressive schemes at randomization (intention-to-treat analysis).

Table 2. Causes of graft failure in 65 patients assigned to receive CsA alone (mono), CsA + steroids (dual), or CsA + steroids + azathioprine (triple)

Cause	Mono	Dual	Triple
Acute rejection	4	5	1
Chronic allograft nephropathy	13	15	11
GN recurrence	3	1	3
Arterial thrombosis	1	—	2
Neoplasia	1	—	1
Infections	—	1	—
Urological	1	1	1
Total (n = 65)	23	23	19

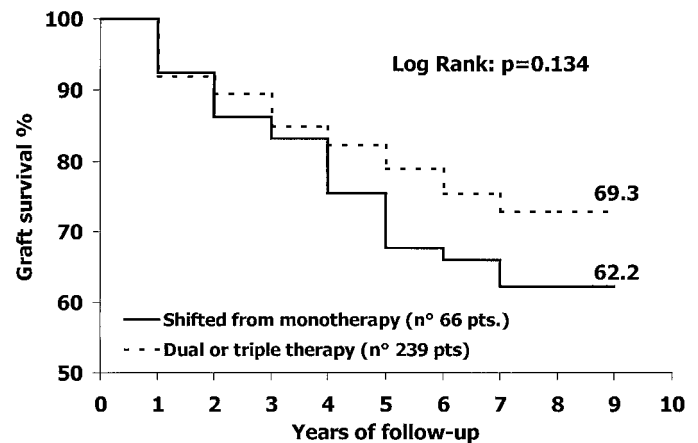


Figure 3. Actuarial graft survival in the 66 patients randomized to monotherapy but shifted to another therapeutical scheme because of inadequate immunosuppression, compared with the actuarial graft survival in all the 239 patients randomized to dual and triple therapy.

months or years after transplantation, mostly because of acute rejection in mono- and dual therapy or because of side effects in triple therapy. Only minor changes were made after the fourth year. The actuarial graft survival in patients randomized to receive CsA monotherapy but shifted later to another treatment because of inadequate immunosuppression was significantly lower than that of the patients who remained in monotherapy (62.2% versus 87.7%; log rank,  $P = 0.004$ ) but was not statistically different from that of patients randomized to receive dual and triple therapy (62.2% versus 69.3%; log rank,  $P = 0.134$ ) (Figure 3).

The mean creatinine clearances in 50 mono-, 45 dual, and 52 triple therapy patients, according to the intention-to-treat principle, were not significantly different among the three groups (Figure 4). The analysis was stopped at 7 yr because of the reduced number of complete observations available after that time. Although slightly lower in the monotherapy group during the whole period, the slopes remained relatively stable over time. Comparing the mean creatinine clearances of patients who remained in monotherapy with those of patients shifted from monotherapy to other regimens, there was a trend toward a slightly better value, even if NS, for those patients who remained in monotherapy (Figure 5).

Significantly more cataracts ( $P = 0.000$ ), more severe osteoporosis as evaluated through computerized mineralometry ( $P = 0.000$ ), and cardiovascular complications ( $P = 0.004$ ) were observed in patients given dual or triple therapy than in patients on monotherapy (Figures 6 and 7). In the dual therapy arm, significantly more infectious episodes ( $P = 0.047$ ) were observed, compared with the mono- and triple therapy arms, although more patients on monotherapy had tremors ( $P = 0.032$  versus dual therapy). Gingival hypertrophy was more frequent in monotherapy than in the triple therapy group ( $P = 0.000$ ) but was as frequent as it was in the dual therapy group ( $P = NS$ ). Twenty-five cases of neoplasia occurred; of them, 19 developed before the fourth year and 6 between the fourth and ninth year (two in patients on monotherapy, one on dual therapy, and three on triple therapy).

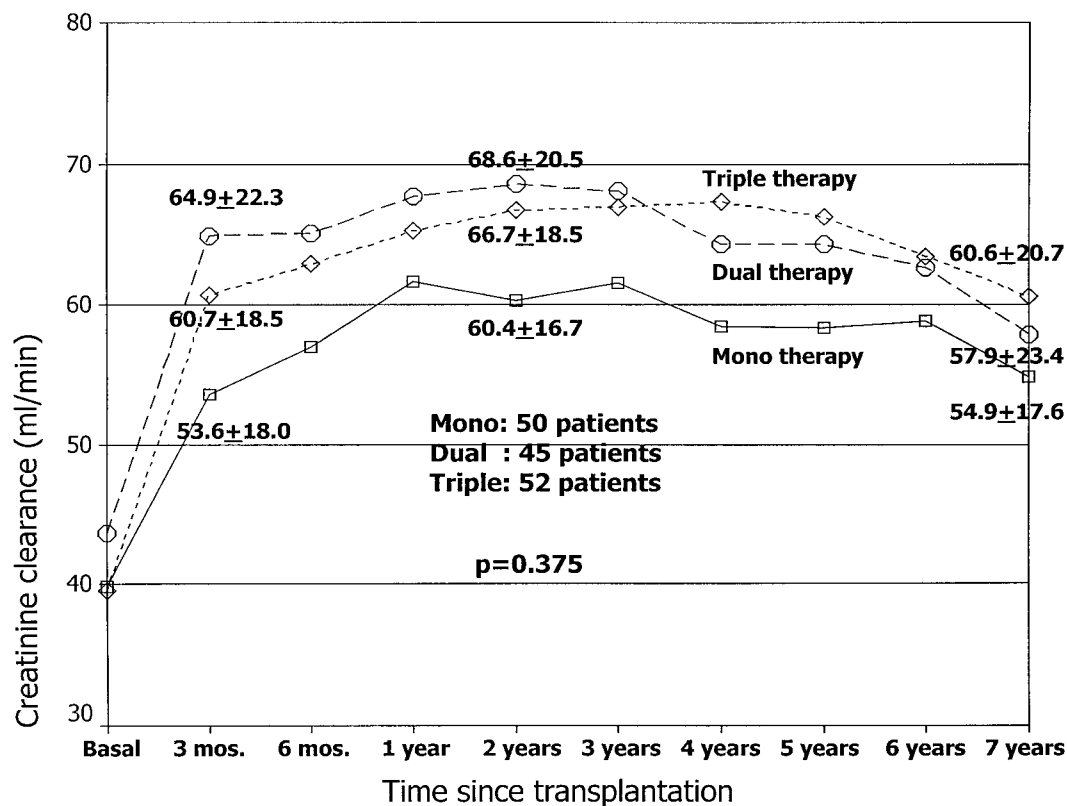


Figure 4. Mean creatinine clearances in the 50 monotherapy, 45 dual therapy, and 52 triple therapy patients, according to the intention-to-treat principle, for whom data up to the seventh posttransplant year were available.

## Discussion

A dual therapy with CsA and corticosteroids has made it possible to reduce the risk of acute rejection and to improve the graft survival in organ transplantation (4–6). Yet chronic allograft dysfunction, either due to immunological factors or CsA toxicity (7,8) and death (9), still remain the main causes of late failure in cadaveric renal transplantation. A triple therapy with steroids, azathioprine, and lower doses of CsA has been suggested to reduce CsA toxicity. However, a meta-analysis of seven randomized controlled trials did not show any advantage of triple therapy over dual therapy in terms of patient or graft survival (10). As an alternative, a steroid-free immunosuppression has been proposed to reduce some life-threatening complications favored by steroids. However, a recent meta-analysis of nine randomized trials pointed out that stopping corticosteroids after months or years after transplantation may expose patients to an increased risk of graft failure (11). This increased risk might be related to the development of late rejections after steroid withdrawal, although the same meta-analysis showed that cyclosporine withdrawal was also associated with acute rejection but with no deleterious effects on long-term allograft function. Other investigators used CsA monotherapy immediately after transplantation. Good results were obtained, but the follow-ups were short in the few randomized studies (12–20).

In this study, we have updated the results of a multicenter randomized trial started in 1990 to evaluate the long-term

results of three different regimens with CsA. To avoid the risk of early failures due to accelerated rejection or nonviable kidneys, we excluded patients with preformed humoral antibodies, posttransplant anuria, or rejection within the first 5 d posttransplant, because in these conditions, CsA alone did not offer good results (18). According to the intention-to-treat analysis, the group of patients assigned to receive monotherapy showed the lowest death rate. Although the difference with the other two groups was NS, the cumulative incidence of deaths was less than half when compared with dual or triple therapy. Of some interest, only two patients of those who remained in monotherapy died during the period of observation. Moreover, only 1 of 115 patients assigned to monotherapy died of cardiovascular disease *versus* 10 of 239 patients assigned to dual or triple therapy. In spite of the low number of fatalities, these data would confirm the deleterious role of corticosteroids in favoring life-threatening complications (21–23).

It has to be pointed out that, however administered, CsA gave excellent results in this series of selected cadaveric renal transplant recipients. The actuarial 9-yr graft survival rate was 70.6%, and the graft half-life was 18.1 yr. The long-term graft survival was similar in the three arms of the study. This result may appear surprising because the monotherapy group showed a significantly higher incidence of acute rejections than the dual or triple therapy groups. A number of studies have outlined the importance of acute rejection as a predictor of an unfavorable outcome in the long term (24–27). However, it has



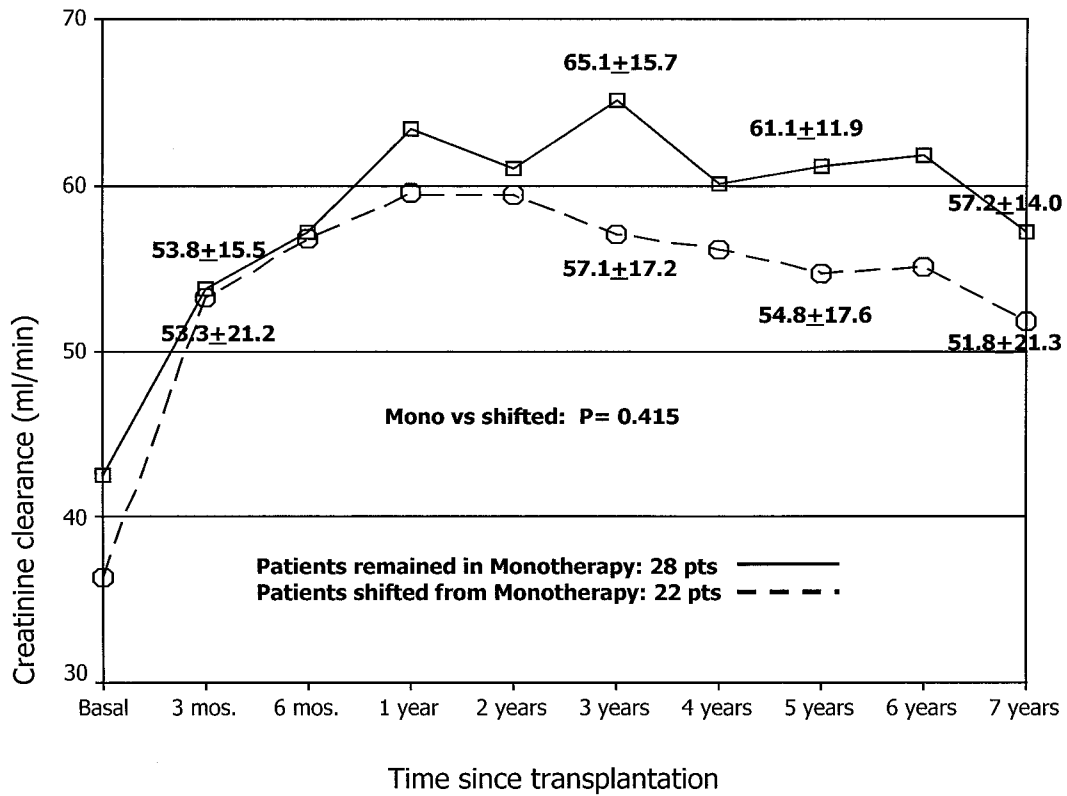


Figure 5. Mean creatinine clearances in the 28 patients who remained in monotherapy versus the 22 patients randomized to monotherapy but shifted to other schemes due to inadequate immunosuppression.

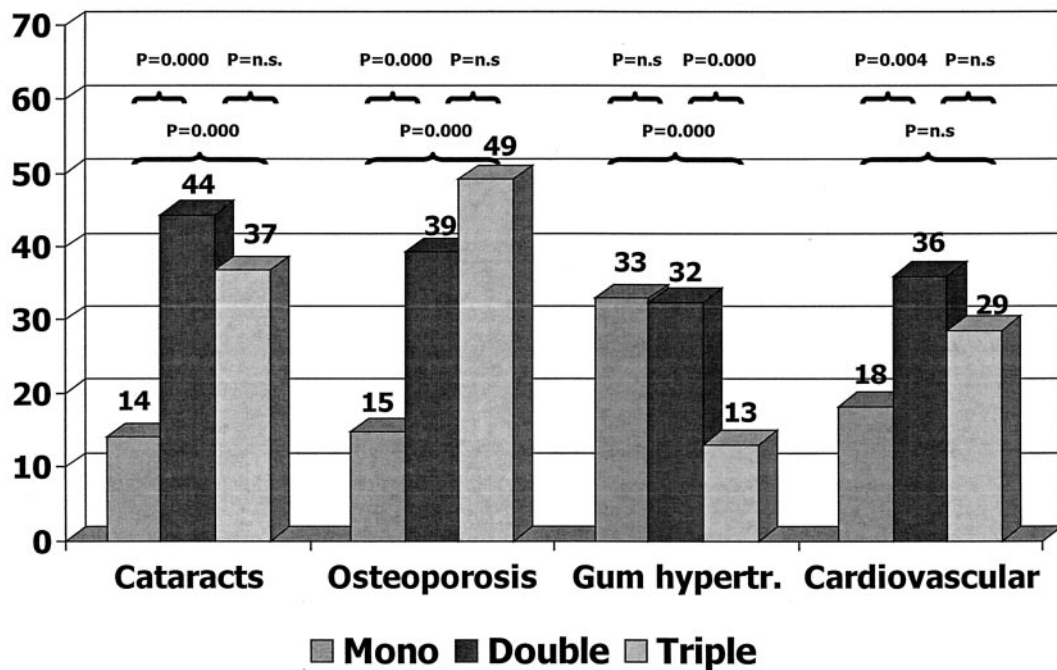


Figure 6. Incidence of complications in the three groups, according to the intention-to-treat principle.

also been pointed out that, when acute rejection is completely reversed by treatment, it does not lead to any deleterious consequence in the long term (26). In our experience, the

diagnosis of acute rejection was easy in patients without steroids, and most rejections proved to be mild and completely reversible. Nevertheless, we decided to add corticosteroids to

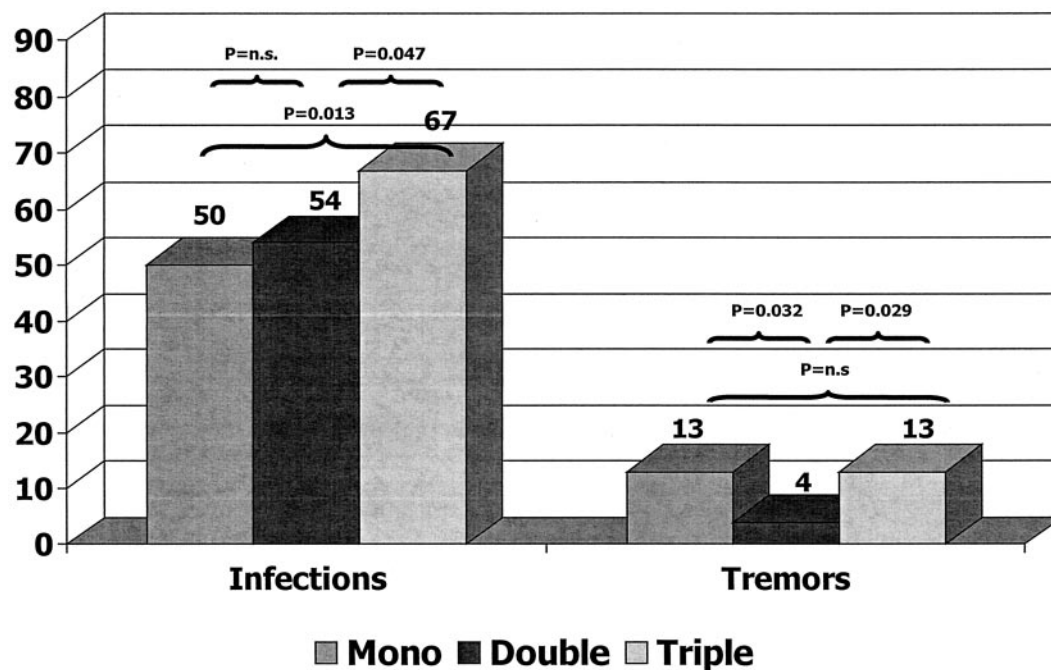


Figure 7. Incidence of complications in the three groups, according to the intention-to-treat principle.

patients who showed more than one acute rejection because we found in another study (28) that two or more rejections were associated with an increased risk of late graft failure.

Again of interest, some of the most disturbing side effects of posttransplant therapy, such as cardiovascular complications, cataracts, and osteoporosis, were significantly less frequent in monotherapy than in the two other arms of the study. Infections were also less frequent in monotherapy and in dual therapy than in triple therapy, which suggests that the addition of azathioprine may further impair the response to infectious agents. On the other hand, gum hypertrophy and tremors were less frequent in triple therapy, in which CsA was used at lower doses. Taken together, these results showed a reduced iatrogenic morbidity in patients assigned to CsA alone rather than to the other two groups.

A concern with the use of CsA monotherapy is the possibility of an increased nephrotoxicity related to the use of higher doses of CsA. In this study, however, we did not find a significant difference in the mean levels of creatinine clearance among the three treatment groups at 7 yr. This result, coupled with the excellent graft half-life of 18.4 yr, would suggest that CsA given as monotherapy does not necessarily expose patients to progressive renal damage. Another concern with CsA monotherapy is that patients who have to add corticosteroids because of repeated acute rejection can be exposed to an increased risk of chronic rejection and late failure. We actually found a worse long-term outcome in monotherapy patients to whom steroids had been added to the therapy than in those who continued without, which confirms previous results of a monocentric study (29). However, in the long term, the graft survival was similar in the subgroup of patients to whom steroids were added and in the group of patients assigned to dual or triple

therapy as a whole. These data show that starting with a steroid-free immunosuppression did not penalize cadaveric transplant recipients in this series.

In conclusion, patient selection seems to be of paramount importance in assuring optimal results in the long term. In this context, no immunosuppressive scheme seems better than another in terms of graft survival. However, CsA monotherapy, by reducing the incidence of side effects and the patient mortality rate, may offer substantial advantages over the other two regimens, provided that acute rejections are promptly recognized and treated. It is hoped that the newer immunosuppressive drugs that may allow a reduction of the doses of CsA and an increase in the number of patients with whom corticosteroids can be eliminated will be able to further improve the long-term graft survival and the quality of life of renal transplant recipients.

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