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Costs of drugs used after renal transplantation

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Abstract There are no detailed data on the relative contributions to overall health care costs of the various drugs that are commonly used in renal transplant patients. We performed a cost analysis in 122 patients, using the medical records and our hospital administration service as data sources, for all health care-related costs during the first year after renal transplantation. During the first 3 months all patients were on cyclosporine (CsA) and prednisone. Subsequently, they were randomly allocated to CsA monotherapy or to conversion from CsA to azathioprine. Cost of drugs comprised about 25 % of total health care expenses. In CsA-treated patients, the following costs per patient per year were calculated: CsA, DFL 9929 (1 DFL is about US $ 0.60; 67.5 % of total drug costs); antilymphocyte agents, DFL 2613 (17.8 %); other immunosuppressive drugs, DFL 455 (3.1 %); antimicrobial agents, DFL 687 (4.7 %); antihypertensive drugs, DFL 467 (3.2 %); remaining drugs, DFL 554 (3.8 %). Conversion from CsA to azathioprine resulted in a decrease in mean drug costs for the remainder of the first posttransplant year of DFL 4597 ($P < 0.01$). Although the incidence of acute rejections tended to be higher after steroid withdrawal than after conversion (39 % versus 26 %, not significant), the costs of anti-rejection therapy, hospitalization, and laboratory services did not differ. We conclude that CsA is the main determinant of overall drug costs. When compared to CsA monotherapy, conversion from CsA to azathioprine at 3 months after transplantation may result in subsequent cost savings of about DFL 5000 per patient per year without a higher incidence of rejection or graft loss.

Key words Renal transplantation · Cost analysis · Cyclosporine · Immunosuppressive drugs

Introduction

Costs of drugs, especially cyclosporine (CsA) and antilymphocyte agents, considerably add to overall expenses of health care in renal allograft recipients. Detailed data on the relative contribution of various drugs to health care expenditure in this population are not available. We performed a cost-effectiveness analysis in renal transplant patients who participated in a prospective randomized trial comparing CSA monotherapy with the combination of azathioprine and prednisone from 3 months after transplantation. The data that were gathered for this analysis during the first year after transplantation allowed us to answer the following questions:

1. How do the costs of drugs compare to the costs of other items (e.g., hospital admission days, laboratory services)?
2. What is the relative contribution of various classes of drugs to total drug costs?

3. How do different immunosuppressive regimens affect costs of drugs and of other items?

Patients and methods

Patient population and treatment protocol

Our study population comprised 127 recipients (age between 18 and 65 years) of a first or second cadaveric renal allograft, with a functioning graft at 3 months after transplantation. None of the patients had received induction therapy with antilymphocyte agents. CsA was given in an oral dose of 12 mg/kg per day during the first month. This was gradually reduced to about 4 mg/kg per day at 3 months after transplantation. The prednisone dose was 25 mg/day during the first month and 20 mg/day during the second and third months after transplantation. At 3 months after transplantation, patients were allocated to withdrawal of steroids, resulting in CsA monotherapy, or to replacement of CsA by azathioprine. In the CsA group, CsA was continued in the same dosage with adjustments to reach trough blood levels between 100 and 200 ng/ml (monoclonal antibody assay). The daily prednisone dosage was reduced by 5 mg every 2 weeks, resulting in CsA monotherapy after 6 weeks. In patients allocated to azathioprine-prednisone therapy, CsA was replaced without overlap by azathioprine at a dosage of 3 mg/kg. Their prednisone dosage was temporarily increased from 20 to 25 mg/day and reduced by 5 mg every 2 weeks until a maintenance dose of 10 mg/day was reached. Antimicrobial prophylactic therapy was not applied, but all patients received an H_2-receptor antagonist during the first 3 to 4 months after transplantation as prophylaxis against peptic ulcers.

During the first 3 months after transplantation, acute rejection episodes were treated with methylprednisolone (1 g/day i.v. on 3 consecutive days) or antithymocyte globulin (ATG, RIVM Bilthoven, The Netherlands; 200 mg/day i.v. on alternate days for 10 days). An oral course of high-dose prednisone (initial dosage 200 mg/day tapering to 25 mg/day in 12 days) was given after failure of one or both of these treatments. From 3 months after transplantation (i.e., after randomization), acute rejections were primarily treated with ATG in all cases. High-dose prednisone courses were given in case of failure of ATG, bone marrow suppression, or previous treatment with ATG for rejection. Occasionally, acute rejections were treated with monoclonal anti-CD3 antibodies.

Cost analysis

Health care costs were calculated for the first year after transplantation. Costs of kidney-acquisition and indirect costs for society, e.g., costs related to disablement, were not considered. Otherwise, no restrictions were made in the services that were included, regardless of the probability of a relationship between a particular service or activity on the one hand and the renal transplantation on the other hand. The medical records were used as data source for the amounts of all kinds of drugs that were used during hospital stays (except drugs used in the operating room) as well as on an outpatient basis. Similarly, number of admission days, number of visits to the outpatient clinic, and number of CsA blood level measurements were counted from the medical records. The clinical laboratory and blood transfusion service supplied quantitative information on their services for the patients concerned. Our hospital financial administration service provided data on activities regarding to following items: operating room and anesthesia, diagnostic radiology, nuclear medicine, endoscopy, pathology, and physiotherapy. Prices current during 1993 or 1994, and expressed in Dutch guilders (1 DFL is about U.S. $ 0.60), were used to calculate costs.

Table 1 Health care costs per patient during the first year after transplantation in patients who were allocated treatment with cyclosporine monotherapy *(CsA)* or a combination of azathioprine and prednisone *(Aza-Pred)*. Costs are expressed in Dutch guilders (means ± SD)

Item	Treatment period (months)	CsA	Aza-Pred
Drugs	1–3	5641 ± 2598	5829 ± 2677
	4–12	9064 ± 4713	4280 ± 4062*
	Entire year	14706 ± 5361	10109 ± 4680*
Hospitalization	1–3	8311 ± 4692	8036 ± 4351
	4–12	10520 ± 30609	5579 ± 8925
	Entire year	18831 ± 31444	13615 ± 10159
Visits to outpatient clinic	1–3	816 ± 189	852 ± 185
	4–12	1554 ± 597	1499 ± 449
	Entire year	2370 ± 625	2351 ± 502
CsA level measurements	1–3	965 ± 365	1020 ± 387
	4–12	1009 ± 459	173 ± 347*
	Entire year	1975 ± 675	1194 ± 495*
Renal replacement therapy	1–3	551 ± 1316	374 ± 881
	4–12	109 ± 788	35 ± 273
	Entire year	660 ± 1497	409 ± 908
Laboratory services (excluding CsA level measurements)		9453 ± 7352	8516 ± 3207
Other diagnostic and therapeutic activities		4944 ± 3882	4335 ± 4425
Blood products		545 ± 1168	355 ± 571
Total costs		53484 ± 44828	40882 ± 18895**

* $P < 0.001$, ** $P < 0.05$ for differences between both groups

Prices of the medication that was used were obtained from the hospital pharmacy. The direct costs of hospital days and visits to the outpatient clinic were estimated on the basis of personnel costs and material expenses (excluding medication and blood products) and amounted to about DFL 300 and DFL 75, respectively. For the intensive care unit, costs were estimated at DFL 2000 per day. The costs of other services were assessed in an analogous way and in case reliable estimations were not attainable (as for laboratory services), charges were used as a proxy for costs.

Statistical analysis

Although a number of patients switched from one treatment to another (e.g., because of CsA nephrotoxicity), all data were analyzed on an intention-to-treat basis. Calculations were performed with the SAS system (SAS Institute, Cary, North Carolina, USA). Data are given as means with SD. Comparisons of numerical data were performed with Wilcoxon's rank sum test. Proportions were compared with chi-square analysis using continuity correction. A P value smaller than 0.05 was considered statistically significant.

Results

Two patients who died, two patients with graft loss, and one patient for whom insufficient data were available, were excluded from the analysis (death and graft loss were evenly distributed among both groups). Of the re-

Table 2 Costs of various classes of drugs that were used during the first year after transplantation by patients who were allocated treatment with cyclosporine monotherapy *(CsA)* or a combination of azathioprine and prednisone *(Aza-Pred)* from 3 months after transplantation. Added costs for all patients in each group are expressed in Dutch guilders

Drug	Treatment period (months)	CsA ($n = 61$)		Aza-Pred ($n = 61$)	
		Absolute	Percentage of total	Absolute	Percentage of total
Cyclosporine	1–3	238083		249920	
	4–12	367597		48694	
	Entire year	605680	67.5	297985	48.3
Azathioprine	1–3	1453		1168	
	4–12	19842		63719	
	Entire year	21296	2.4	64888	10.5
Prednisone	1–3	2078		2083	
	4–12	2583		3087	
	Entire year	4662	0.5	5170	0.8
Antilymphocyte agents	1–3	73716		75425	
	4–12	85720		82421	
	Entire year	159436	17.8	157847	25.6
Steroids for rejection	1–3	1028		1307	
	4–12	741		380	
	Entire year	1770	0.2	1687	0.3
Antihypertensive drugs	1–3	5251		4386	
	4–12	23251		17966	
	Entire year	28502	3.2	22353	3.6
Antimicrobial agents	1–3	13323		14683	
	4–12	28574		29907	
	Entire year	41898	4.7	44591	7.2
Other drugs	1–3	9164		7191	
	4–12	24616		14908	
	Entire year	33780	3.8	22099	3.6
Total	1–3	344104		355540	
	4–12	552932		261088	
	Entire year	897037	100	616629	100

maining 122 patients, the mean age was 43 ± 13 years, 64 % were male, and 83 % had a first transplant. Each treatment group consisted of 61 patients. The number of patients with one or more acute rejection episodes during the first 3 months after transplantation did not differ between the groups (CsA: 25 %, azathioprine-prednisone: 26 %). From the time of randomization until the end of the first posttransplant year, the incidence of at least one rejection was 39 % in the CsA group and 26 % in the azathioprine-prednisone group (not significant).

Table 1 shows the costs of drugs and of several other items for all patients, and for both treatment groups separately. When available, separate data are given for months 1–3 and months 4–12 after transplantation. Costs of drugs comprised about 25 % of all expenses to health care during the first year after transplantation in these patients. As expected, in 62 patients who experienced one or more rejection episodes during the first year after transplantation, total costs per patient were significantly higher than in 60 patients without a rejection (DFL 56717 ± 39406 versus 37333 ± 26250; $P < 0.001$). When patients with any acute rejection episode after transplantation were excluded from calculations, total costs were DFL 43582 ± 34398 in the CsA group ($n = 28$) and DFL 31865 ± 14654 in the azathioprine-prednisone group ($n = 32$) ($P < 0.05$).

In Table 2, costs of different classes of drugs are summarized. In the CsA group, whole-year costs of CsA made up 68 % of all drug costs, as compared to 48 % in the azathioprine-prednisone group. When only the period after randomization was included in the calculations (months 4–12), these figures were 67 % and 19 %, respectively. Antilymphocyte agents formed the next most expensive drug category. The costs of drugs other than immunosuppressive agents amounted to only 10–15 % of total drug costs during the first year after transplantation.

The lower total costs in the azathioprine-prednisone group (Table 1), in part, resulted from significantly lower drug costs and less expenditure on measurements of CsA levels. During the 9 months after randomization, the costs of base-line immunosuppressive therapy (CsA, prednisone, and azathioprine) differed significantly between groups, despite the inclusion of patients who changed from one treatment group to the other at some time (CsA, DFL 6394 ± 274; azathioprine-prednisone, DFL 1893 ± 192; $P < 0.001$). From the data obtained during the last 3 months of the first posttransplant year, we estimate that conversion from CsA to

azathioprine might result in subsequent savings of about DFL 4700 per year.

Discussion

Drugs substantially contribute to the costs of renal transplantation. In our population of renal transplant patients, drugs accounted for about 25 % of the financial expenses to health care during the first year after transplantation. Together with a decrease in the number of hospital admission days, the relative contribution of drugs to total costs can be expected to be even larger during subsequent years. CsA is the main determinant of overall drug costs, since costs of CsA amounted to nearly 70 % of all drug costs in CsA-treated patients.

We recognize that these figures cannot be generalized to all renal transplant patients. First, a number of the criteria included (only first and second transplants, age between 18 and 65 years) may have caused some selection bias. Second, only the data of patients who were alive with a functioning graft at 1 year after transplantation were analyzed. Some of the patients with severe or multiple complications, ultimately leading to death or graft loss, may generate unusually high or low costs on certain items. In addition, it has to be mentioned that for several entries in our calculations, hospital charges were used as a proxy for costs. In some instances these charges can at best be used as a rough estimate of how the costs of comparable activities (e. g., different laboratory services) relate to each other. Nevertheless, we believe that our data provide valuable information, which is currently scarce, on the relative contribution of various drugs and other services to the costs of renal transplantation.

The use of CsA has substantially increased graft survival rates after renal transplantation [2, 3]. This improvement in graft survival appears to result mainly from a decrease in the number of rejection episodes during the first months after transplantation. From an economic point of view, switching from CsA to azathioprine at some time after transplantation seems an attractive treatment strategy. In our hands, azathioprine-prednisone from 3 months after transplantation appeared to be a more cost-effective treatment than CsA monotherapy. The tendency to a higher frequency of rejections in the CsA group could not sufficiently explain the higher costs in this group, since the difference in costs remained present after exclusion of patients with one or more rejection episodes from both groups. Previous studies have demonstrated the cost-effectiveness of CsA-containing immunosuppressive regimens [1, 6]. However, in these studies, control patients did not receive CsA at all, whereas in the current study all patients were treated with CsA during the first 3 months after transplantation. This initial treatment with CsA protected our patients from the high risk of rejection and associated costs of hospital readmissions during the early phase after transplantation. Indeed, the finding of lower costs associated with the use of CsA in the study of Showstack et al. [6] was confined to the direct posttransplantation hospitalization period, while total charges did not differ from those in the control group during the follow-up period.

Our data do not allow a comparison of the cost-effectiveness of conversion from CsA to azathioprine versus continued treatment with CsA and prednisone. Given the impression that a number of rejections in our CsA group were related to the withdrawal of steroids, continued treatment with both CsA and prednisone will most likely result in a rejection incidence that is lower than that observed after conversion from CsA to azathioprine [5]. In that case, the reduced frequency of rejections may compensate for the higher costs of base-line immunosuppressive therapy. Nevertheless, recent reports of similar graft survival rates after conversion from CsA to azathioprine as compared to continued treatment with CsA and prednisone [4, 5], support a deliberate use of a conversion regimen, which may save about DFL 5000 per patient per year.

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