Renal Transplant Recipient Response to a Cyclosporine Use Survey at Two Canadian Transplant Centres

Nancy M. Waite, Ingrid Sketris, Krista Grobler, Michael West and Sheila Gerus

ABSTRACT

Kidney transplantation has significantly improved the quality of life for patients with end-stage renal disease. To gain a better understanding of kidney transplant patients' demographics and perspectives about their drug therapy, 361 kidney transplant recipients from two regional transplant centres completed a self-report questionnaire. The patients who responded (73%) were 60% male, 46 ± 13 years, 71% had received their kidney from a cadaveric source and 61% were greater than three years post transplant. Further demographics identified included country of origin, language of preference, level of education, number of rejections, and self-perception of health. The median dose of cyclosporine was 2.9 mg/kg/day (mean = 3.5 ± 3.9 mg/kg/day) with the majority of patients receiving the capsule formulation. The mean number of prescription medications taken by recipients was 4.5 ± 2.1 (excluding cyclosporine) with cadaveric transplant patients receiving significantly more medications than live donor recipients ($p<0.01$). Females reported significantly more side effects (1.9 ± 1.7) than males (1.5 ± 1.3) ($p=0.01$). Overall, 24% of patients reported one side effect associated with cyclosporine, 23% two, 9% three, and 9% four or more. Eighty-three percent of patients felt that they received an adequate amount of information and instruction about their medications while in hospital and 76% felt they received an adequate amount in follow-up clinic. Patients requested more information about side effects, drug interactions, general up-to-date drug information and assistance with scheduling difficulties. This study provides pharmacists with information regarding patient demographics and perspectives on their drug therapy which will assist them with providing pharmaceutical care to kidney transplant patients.

Key words: *cyclosporine, kidney transplant, survey, transplant recipients*

RÉSUMÉ

La greffe du rein a grandement amélioré la qualité de vie des patients atteints d'insuffisance rénale terminale. Pour mieux comprendre les caractéristiques démographiques et les perspectives relatives aux traitements médicamenteux des patients qui ont reçu une greffe rénale, 361 receveurs de greffe de rein de deux centres de greffe régionaux ont répondu à un questionnaire d'auto-évaluation. Parmi les répondants (73 %), 60 % étaient des hommes (âgés de 46 ± 13 ans), 71 % avaient reçu un rein provenant d'une personne décédée et 61 % avaient reçu leur greffe depuis plus de trois ans. Parmi les autres caractéristiques démographiques relevées, on note le pays d'origine, la langue utilisée, le degré d'éducation, le nombre de rejets et la perception individuelle de la santé. La dose moyenne de cyclosporine reçue était de 2,9 mg/kg/j (moyenne = 3,5 ± 3,9 mg/kg/j), sous forme de capsule pour la majorité des patients. Le nombre moyen de médicaments d'ordonnances (à l'exclusion de la cyclosporine) consommés par receveur de greffe était de 4,5 ± 2,1; les patients qui avaient reçu un rein provenant d'une personne décédée prenaient considérablement plus de médicaments que ceux qui avaient reçu un rein d'une personne vivante ($p < 0,01$). Les femmes ont signalé avoir beaucoup plus d'effets indésirables (1,9 ± 1,7) que les hommes (1,5 ± 1,3) ($p = 0,01$). Dans l'ensemble, 24 % des patients ont dit avoir éprouvé un effet indésirable associé à la cyclosporine, 23 % deux effets indésirables, 9 % trois et un autre 9 % quatre effets indésirables ou plus. En outre, 83 % des patients ont dit avoir reçu suffisamment de directives et de renseignements pertinents sur les médicaments qu'ils prenaient à l'hôpital et 76 % en ont jugé de même en ce qui concerne leur suivi en clinique. Cependant, les patients ont demandé davantage

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de renseignements en matière d'effets indésirables, d'interactions médicamenteuses, de mise à jour générale sur les médicaments et d'aide en cas de problèmes d'horaire. La présente étude fournit au pharmacien des renseignements démographiques et de nouvelles données sur les traitements médicamenteux des patients qui ont reçu une greffe de rein, qui l'aideront à prodiguer les soins pharmaceutiques à ces patients.

Mots clés : *cyclosporine, greffe de rein, sondage, receveurs de greffe*

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INTRODUCTION

Renal transplantation is a cost-effective method of improving the quality of life for patients with end-stage renal disease.[1] Patient outcomes following renal transplantation have improved over the last 10 years. Rejection rates have declined, primarily due to the availability of more effective anti-rejection medications such as cyclosporine.[1] While effective, cyclosporine has numerous side effects, significant cost and intensive monitoring requirements, which have been well documented in the literature.[2,3] However, no studies, that the authors are aware of, have examined the patient's perspective on such issues as preferences for cyclosporine formulation, method of distribution, and satisfaction with the information and instruction they receive regarding their medication. Although large data banks collect information on kidney transplant patients,[4] a profile which includes reported side effects, cyclosporine dosage, country of origin, language of preference, education level, etc. is not available. Understanding the characteristics of the patients and their perspectives regarding their drug therapy will assist pharmacists when providing pharmaceutical care and patient education to this population. Therefore, this study had three objectives. First, to collect general information on kidney transplant recipients' demographics, cyclosporine regimens, and concomitant medications. Secondly, to examine patients' perspectives about cyclosporine formulation, side effects, and method of distribution; adequacy of information and instruction regarding medication; and perceived health status. Finally, to identify recipients' medication-taking behaviour and to assess their adherence to their medication regimen. The results of the final objective, assessment of patient compliance, have been published elsewhere.[5]

METHODS

A self-report questionnaire was developed. Two preliminary questionnaires were pretested on 16 recipients from the McGill Transplant Centre in Montreal and then 90 participants in the Canadian Transplant Games. The questionnaire was sent to 513 renal transplant recipients taking cyclosporine (256 at Victoria General Hospital, Halifax and 257 at St. Michael's Hospital, Toronto). The final questionnaire, consisting of 31 questions (available from the authors upon request), was mailed August 3, 1993 along with a cover letter that outlined the purpose of the study, assured anonymity, and provided a contact telephone number for clarification of questions. It consisted of questions relating to demographics, health status, liquid versus capsule formulation, cyclosporine dosage regimen, cyclosporine side effects, method of delivery, compliance, adequacy of amount of information and instruction, and a general comments section. All renal transplant patients who received cyclosporine from the pharmacy department at the Victoria General Hospital and St. Michael's Hospital were included in the study. The Victoria General Hospital site included all Nova Scotia and Prince Edward Island patients, and all Newfoundland patients who were followed at the Cornerbrook Centre (those followed at the St. John's Centre were excluded). A reminder letter was sent eight weeks later.

Medication teaching at both sites was done according to protocols approved by the respective transplant teams.[6,7] Victoria General Hospital's program was taught by nurses who distributed a booklet which contained information on medications, including two pages on cyclosporine. At St. Michael's Hospital a booklet and audiotape about transplant medication was given to the patients and then a pharmacist reviewed the information with them. A post-test was given as part of the self-medication program. Both centres had an informal outpatient medication teaching program.

Statistical analysis was performed using ABTAB (Bruce Bell and Associates, Canon City, Colorado). Mean values (reported as mean ± SD) between the two groups were assessed using an unpaired t-test, and frequency of occurrence was compared using chi-square analysis. A p-value of <0.05 was considered significant.

RESULTS

Patient Characteristics

One hundred and eighty-two renal transplant recipients from Victoria General Hospital and 179 from St. Michael's Hospital responded to the questionnaire. After accounting for 16 questionnaires returned to sender, the overall response rate was 73%. Respon-

dents were 60% male, with a mean age of 46 ± 13 years, and 71% had received kidneys from a cadaveric source. The majority of patients listed their country of origin as Canada (85%), with 29 different countries listed for the remaining respondents. Regional differences were apparent with 58% of St. Michael's Hospital patients reporting Canada to be their country of origin compared to 95% of patients from Victoria General Hospital. Language of preference was English for 95% of recipients and was similar in both hospitals. Other languages of preference included French, Portuguese, Chinese, Italian, and Spanish. Thirty-three percent of respondents had college education or more, 60% high school education, and 7% elementary school education. The mean number of years of education was 11.7 ± 3.8. The time since transplant when surveyed was less than one year for 16% of recipients, 1 to 2.5 years for 23%, 3 to 5.5 years for 32%, and 6 years or more for 29%. Seventy-four percent of recipients reported that they did not have any rejections, 8% had had one, 15% two or more, and 3% didn't know how many. Self-perception of health was excellent in 14% of patients, very good in 35%, good in 31%, poor to fair in 18%, and 2% had no response.

Cyclosporine Use

The median dose of cyclosporine was 2.9 mg/kg/day, with the mean dose being 3.5 ± 3.9 mg/kg/day (no significant difference was found between sites). The majority of patients took cyclosporine in capsule formulation (94%). Significantly more patients from Victoria General Hospital (9%) took liquid than patients from St. Michael's Hospital (2%) ($p<0.05$). Of the 160 who had tried both liquid and capsule formulations, 96% preferred the capsule and 77% felt that the capsule helped them maintain their schedule. The reasons for preference of liquid versus capsule are shown in Figure 1. Seventy percent of recipients picked up their cyclosporine at the hospital with the remaining patients receiving their cyclosporine by mail. Respondents from Victoria General Hospital were more likely to receive cyclosporine by mail (66%) than those from St. Michael's Hospital (4%)($p<0.05$). Seven patients complained of problems with mail delivery including the cost of delivery, damage or loss of shipment, and misplaced shipments.

Concomitant Medications

Fifty-five percent of recipients were receiving triple therapy with cyclosporine, azathioprine and prednisone, 23% double therapy with cyclosporine and prednisone, 3% double therapy with cyclosporine and azathioprine, and 18% cyclosporine alone. Patients from St. Michael's Hospital were more likely to receive triple therapy (74%) than patients from Victoria General Hospital (37%) ($p<0.01$). On average, patients were taking 4.5 ± 2.1 medications (excluding cyclosporine) with 34% taking zero to three medications, 29% four to six medications, and 37% seven or more medications. Patients at St. Michael's Hospital took significantly more medications other than cyclosporine (4.9 ± 1.9) than patients at Victoria General Hospital (4.3 ± 2.2) ($p<0.05$). Recipients of cadaveric kidneys took significantly more medications (4.8 ± 2.1) than recipients of kidneys from live donors (3.9 ± 1.7) ($p<0.01$). The types of concomitant medications are shown in Figure 2.

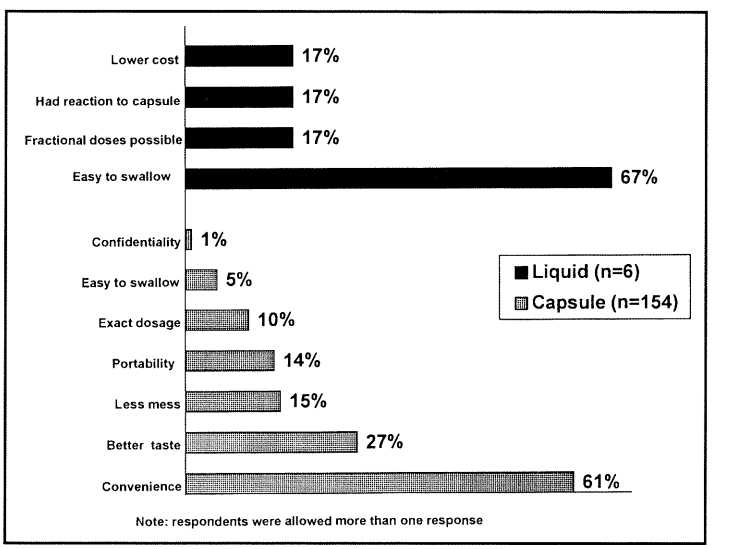

Figure 1: Reasons for Preference of Cyclosporine Formulation

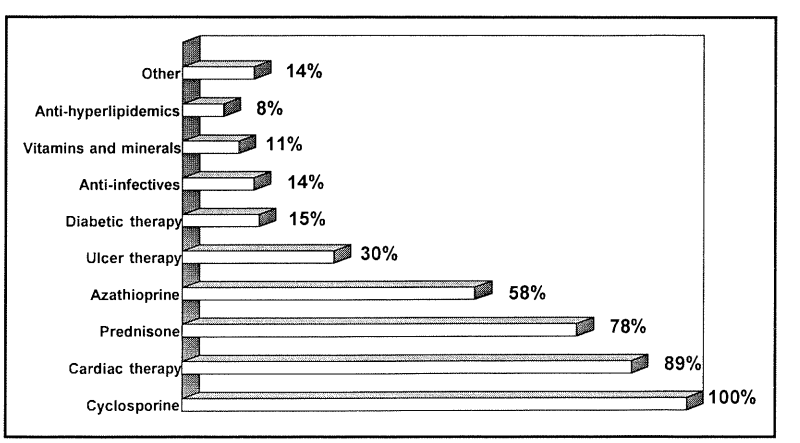

Figure 2: Medication Taken by Transplant Recipients

Side Effects Attributed to Cyclosporine

The number and type of side effects attributed to cyclosporine therapy are shown in Figure 3 and Figure 4. Females reported significantly more side effects (1.9 ± 1.7) than males (1.5 ± 1.3) (p=0.01). Females were also more likely to identify hirsutism as a side effect (46%) than males (29%) (p<0.01).

Information and Instruction about Medication

Eighty-three percent of recipients felt that they received an adequate amount of information and instruction about their medications while in hospital and 76% felt they received an adequate amount in follow-up clinic. There was no difference between the two sites in the adequacy of medication information and instruction as perceived by patients.

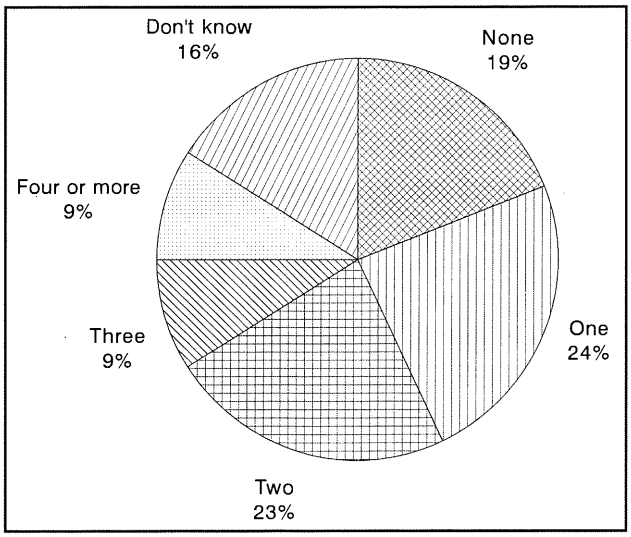

Figure 3: Number of Side Effects Attributed to Cyclosporine

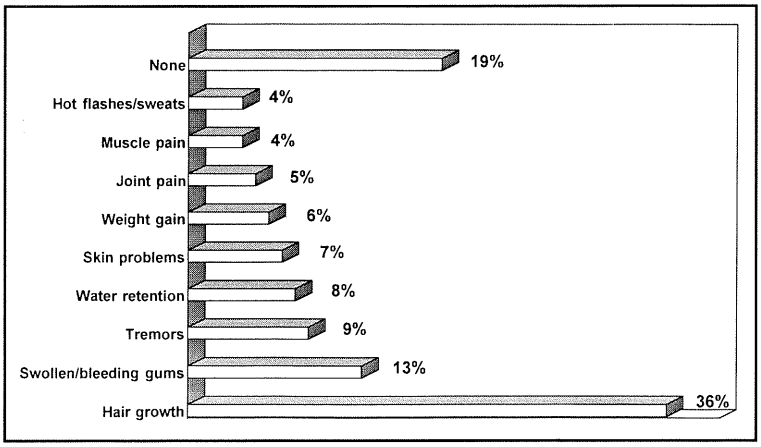

Figure 4: Type of Side Effects Attributed to Cyclosporine

General Comments

When asked for additional comments on how their post-transplant medication regimen could be improved, patients most frequently requested more information on side effects, drug interactions, general up-to-date information and assistance with scheduling difficulties.

DISCUSSION

The lack of organ availability has resulted in a large and growing list of patients waiting for transplants. The number of patients with a functioning kidney transplant continues to increase, but is decreasing as a percentage of the total end-stage renal disease population.[4] Additionally, the number of transplants performed per year has decreased from a peak of 901 in 1988 to the lowest number of 755 in 1992.[4] As a result, approximately 1900 patients are waiting for kidney transplants in Canada.[4] It is important for recipients to maintain a functional graft. The availability of cyclosporine on the Canadian market in 1984, with its ability to decrease the number of rejections, was a significant advance in transplant medicine.[8] However, a large percentage of patients taking cyclosporine experience side effects; the cost of the drug is $5000-6000/year (although free to patients since provincial drug plans pay for 100% of cost); and as a result of a narrow therapeutic window and large intra- and interpatient variability in pharmacokinetics, monitoring of cyclosporine concentrations is required. As cyclosporine is such a critical drug in transplant therapy, the recipient's perspective on taking such a drug is important.

This study examined renal transplant patients' opinions about cyclosporine, characteristics of its administration, and adequacy of information provided to the patients about transplant medications through a self-reported questionnaire. An excellent response rate[9] assisted in providing a large data base of information on cyclosporine use in two regions in Canada.

Patient characteristics may alert the pharmacist to the patient's predisposition to actual or potential problems. For example, patient ethnicity may influence drug response and drug pharmacokinetics[10] and their health beliefs may influence their adherence to medication regimens.[11] As shown in this study, patient background, culture, and language within a region and between regions may be highly variable. Information about education level is important when developing education programs for individual patients or a broader based educational program.[12] This study showed that 67% of transplant recipients had elementary or high school education, and therefore, the language

level within patient teaching programs should be consistent with these data. As well, the majority of education programs are directed at preventing drug-related problems in the newly transplanted population. Since the problem of noncompliance is greater after one year post-transplant,[5] it is important to provide pharmaceutical care and educational opportunities to the large (84%) and growing group of patients more than one year post-transplant.

Although not consistent, a number of studies have shown that taking a large number of medications is also associated with noncompliance.[5,13,14] The majority of respondents take double or triple immunosuppressive therapy plus additional medications resulting in an average of 4.5 drugs per patient (excluding cyclosporine). From the pharmacist's perspective, it is important to ensure that all of these medications are indicated, to screen for drug interactions and adverse effects, to simplify schedules to improve compliance, and to educate recipients about their medications.[15]

Decisions for hospital and provincial formularies regarding cyclosporine formulation (liquid or capsule) should take into consideration factors such as effectiveness, cost, and patient preference. Patient preferences for cyclosporine formulation have not been reported in the literature. In this study, most patients were found to prefer capsules although a few patients preferred liquid for the most common reason that it was easier to swallow. When providing pharmaceutical care, the pharmacist should determine the patient's preference and physical needs (e.g., reduced eyesight or dexterity) regarding formulation (although criteria for funding may also influence choice). As a large proportion of recipients receive their prescriptions by mail (although region specific), mechanisms for communicating regimen changes and providing education to this population must be in place. Community pharmacists have an important role to play, particularly in screening for prescription and nonprescription drug interactions.

Many patients were concerned with side effects, primarily cosmetic ones. While it may not be possible to completely prevent these side effects, recipients need to be fully educated about what side effects to expect, how to minimize them and when to contact their physician. As females reported more adverse effects, and side effects such as hirsutism were of more concern than to males, they may need special counselling. Finally, it is important to consider lowering the dose of cyclosporine, as several side effects are believed to be dose-related. However, caution should be advised to balance minimizing the side effect profile with avoiding acute or chronic rejection secondary to inadequate cyclosporine concentrations.[16-19] In general, respondents to this survey reported a lower incidence of side effects than is reported in the literature.[20] This was probably a result of patients not recognizing that a symptom they were experiencing was related to their drug therapy and the relatively low dose of cyclosporine taken by these patients.

Overall, a large percentage of patients felt they received an adequate amount of information and instruction about their medication while in hospital and in follow-up clinic. However, the comments attached to the survey do indicate recipients have a continuing need for more information, particularly pertaining to side effects, drug interactions, up-to-date information regarding medications, and simplification of medication schedules.

There are a number of limitations to this study's data. Information relied on recipients' self-reporting which was dependent on their memory and honesty. For example, the literature states that 40-50% of patients will experience an episode of rejection.[21] However, only 23% of our patients remembered experiencing a rejection episode. This is not surprising as many of these episodes occur in the first three months post-transplant. No data were collected regarding non-prescription drug use. Since the questionnaire was anonymous, there was no opportunity to correlate reported medication taking behaviour and clinical outcomes. As side effects were not prompted, information collected relied on the recipients' ability to remember side effects and correlate them with cyclosporine use.

Pharmacists need to ensure that they are familiar with the characteristics of their patient population and their patient's preferences and information needs regarding their medication. The pharmacist's approach to the patient when providing pharmaceutical care and more specifically, patient education, should then be tailored accordingly. This study will be of assistance to pharmacists working with kidney transplant patients by providing the background information on this patient population so that the pharmacist can best meet their patient's medication-related needs.

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