

Temporary discontinuation of immunosuppressive treatment and renal graft rejection. Experience of a center in Venezuela

José Herrera,¹ Maribel Chávez,² and Bernardo Rodríguez-Iturbe^{1,2}

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ABSTRACT

In some Latin American countries, discontinuation of treatment when immunosuppressive drugs are unavailable can cause late renal graft loss. This retrospective study reports the frequency and consequences of interrupted treatment at a single center in Venezuela. In 2005 and 2006, we evaluated the medical records of and interviewed 303 patients (181 males) followed for more than one year after renal transplantation done between 1973 and 2005. Noncompliance for > 1 week was reported by 124 patients; 107 (86.3%) instances were due to unavailability of immunosuppressive drugs at the institution (institutional noncompliance), and the remainder were due to voluntary noncompliance. Acute rejection episodes were about three times as frequent among voluntary noncompliers as institutional noncompliers, probably because voluntary noncompliance lasted longer (mean 42.7 ± standard deviation of 14.1 days) than institutional noncompliance (18.5 ± 11.2 days, P < 0.001). Graft loss occurred in 63.6% (7/11) of the episodes of voluntary noncompliance and in 33.3% (10/30) of the episodes of institutional noncompliance. Institutional noncompliance represents a preventable cause of graft loss in some transplantation programs in developing countries.

Key words

Immunosuppression, patient compliance, transplantation, Venezuela.

Renal transplantation is a widely available treatment for end-stage renal disease. Characteristics of the treatment of end-stage renal disease and

transplantation in Venezuela have been reviewed recently (1). Transplanted patients need to be on lifetime immunosuppression regimes, and patient compliance, defined as the extent to which actual treatment coincides with the prescribed treatment (2), diminishes over time and represents a significant cause of graft loss (3, 4). The reported incidence of noncompliance in renal transplanted patients ranges from 2% to 26% (2–8), and is the second most common cause of

renal graft failure, representing 25% of graft losses occurring 2 or more years after renal transplantation (9).

Lack of compliance is generally used to describe a patient behavior that results in unwillingness to follow the prescribed treatment. Other causes of nonadherence to prescribed treatment have been less well studied. The role of economic factors was evaluated by Chisholm et al. (10) in patients who received free immunosuppressive drugs; these authors found that

¹ Renal Service, Hospital Universitario de Maracaibo, Maracaibo, Estado Zulia, Venezuela.

² Centro de Medicina y Cirugía Experimental, Universidad del Zulia, Maracaibo, Venezuela. Send correspondence and reprint requests to: Bernardo Rodríguez-Iturbe, Servicio de Nefrología, 9.º Piso, Hospital Universitario de Maracaibo, Avenida Goajira s/n, Estado Zulia, Maracaibo, Venezuela; e-mail: bernardori@telcel.net.ve

noncompliance was as high as 52% one year after transplantation. Difficulties in access to the clinic were studied by Meyers et al. (11), who concluded that no relationship existed between distance traveled by the patient to the follow-up clinic and compliance.

Another potential cause of nonadherence is the lack of availability of immunosuppressive drugs. Although this possibility is remote in industrialized countries, it cannot be neglected in countries in which transplantation and immunosuppressive treatment are subsidized by the government, and the purchase, control, and distribution of immunosuppressive drugs to patients are centrally controlled. One of these countries is Venezuela, where the vast majority (> 90%) of transplanted patients receive their medications from the Instituto Venezolano de los Seguros Sociales (IVSS). Transplant programs (and patients) outside the capital region, where the central offices of the IVSS are located, do not always receive medications on time to assure seamless availability of posttransplant immunosuppressive therapy. This study analyzes the frequency and consequences of temporary nonadherence to posttransplant immunosuppressive prescriptions resulting from unavailability of immunosuppressive drugs due to operational failures in the distribution system, in patients followed at a single center in Venezuela, in the city of Maracaibo.

METHODS

Patients and data collection

The University Hospital of Maracaibo started its transplant program—the first in Venezuela—in August 1967 (12). This study was done in a selected group of 303 patients followed continuously for one year or more after receiving a kidney transplant in our transplant clinic at the University Hospital between the years 1973 and 2005. Patients transplanted at our center but followed in other clinics and patients who moved out of town were ex-

cluded from this analysis. Data were obtained from a retrospective review of the patients' medical records, and by personal or telephone interview with each patient, done between December 2005 and March 2006. Only instances when one or more immunosuppressive drugs was suspended for one week or more were counted as episodes of nonadherence or interruption of treatment.

The drug distribution system at an IVSS unit operates separately from the follow-up, hospital-based clinic. The category "institutional noncompliance" as listed here indicates that the patient was informed at the IVSS distribution unit that the medication was temporarily unavailable, and the patient reported to the investigators that such was the reason for nonadherence to treatment. If the medication was not available at the IVSS center but the patient was able to obtain the medication by other means (buying it at a pharmacy, borrowing from another patient) the episode was not recorded as noncompliance since the patient took the medication. The frequency with which this situation occurred was impossible to determine because it was not recorded in the medical record or recalled with precision in the telephone interviews. Episodes of institutional noncompliance were compared with episodes in which the patients suspended the medications voluntarily. "Voluntary noncompliance" was determined by the patients' own admission of its occurrence.

Data on acute rejection episodes and the subsequent recovery or irreversible loss of graft function were recorded from the hospital records, and included renal biopsy confirmation.

Statistical analysis

Analysis of variance was used to compare mean values between groups. Contingency tables were used for graft survival, and incidence of rejection was compared by Fischer's exact test. *P* values of < 0.05 were considered statistically significant for differences between groups.

RESULTS

The study concerns 303 patients (181 males, 122 females) who received 186 cadaveric and 117 live donor renal transplants. Mean duration (\pm standard deviation (SD)) of follow-up was 106.5 ± 72.4 months (range 12–396 months). Interruption of immunosuppressive treatment for periods longer than 1 week due to institutional noncompliance occurred in 107 patients, and 17 interrupted immunosuppression voluntarily. Duration of noncompliance was longer in the latter group ($42.7 \pm$ SD of 14.1 days) than in the former ($18.5 \pm$ SD of 11.2 days, $P < 0.001$) and the proportion of rejection episodes related to noncompliance was correspondingly higher among voluntary noncompliers (64.7% vs. 28.0%, $P < 0.001$). The frequency of graft loss related to irreversible rejection was also higher in the group of voluntary noncompliance [33.3% (10/30) vs. 63.6% (7/11), $P < 0.001$].

Only 7.5% (3/40) of the incidences when treatment was interrupted for less than 2 weeks led to graft rejection. In contrast, 45.2% (38/84) of the instances when noncompliance for either cause lasted longer than 2 weeks resulted in rejection episodes.

In this study 251 patients received three immunosuppressive drugs and 52 patients, transplanted prior to 1986, were on double immunosuppression with prednisone and azathioprine. Cyclosporine A was the drug that was interrupted most frequently, followed by mycophenolate mofetil. Rapamycin has been available in Venezuela since 2001 and was prescribed to 24 of the 303 patients in this study. Azathioprine and prednisone were rarely interrupted.

DISCUSSION

Temporary unavailability of immunosuppressive drugs is a cause of nonadherence to treatment in the long-term follow-up of renal transplantation that has not been analyzed previously. The main findings of this study are, first, that 40.9% (124 of 303 patients) of the patients followed for 1 to 33 years after

transplantation had periods of noncompliance. Second, 86.3% of the instances of noncompliance (107 of a total of 124) were due to the temporary lack of available immunosuppressive drugs at distribution units, and episodes of unavailability lasted 18.5 ± 11.2 days. It was not possible to determine why the supply of immunosuppressive drugs ran out without timely replacement in the pharmacies of the institutions in charge of distributing the drugs. The employees in charge, who refused to be identified, declared that the central administration was at fault since the requests and forms were sent in time. Information at the central IVSS offices is not readily available, and those contacted, who

also refused to be identified, declared exactly the opposite. Only 17 patients admitted suspending immunosuppressive treatment by their own choice; this figure is probably a significant underestimate of voluntary noncompliance, since Chisholm et al. (10) reported noncompliance in half of the patients who received free immunosuppressive drugs for longer than one year after transplantation. Finally, we found that acute rejection episodes occurred in 28% of the occasions of institutional noncompliance and caused 33.3% of late (> 1 year) graft loss.

This retrospective study concerned a single center's experience, and therefore the findings may not be generaliz-

able to the entire country or to other countries of Latin America. With these limitations in mind, it is reasonable to suggest that inadequate monitoring of the mechanisms involved in the supply and distribution of immunosuppressive drugs resulted in a preventable cause of late graft loss. Having better-informed patients and greater participation of patients' advocacy organizations are likely to reduce this type of noncompliance.

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RESUMEN

Interrupción temporal del tratamiento inmunosupresor y rechazo del trasplante renal. Experiencia de un centro en Venezuela

En algunos países de América Latina, la interrupción del tratamiento cuando no se dispone de los medicamentos inmunosupresores puede causar la pérdida tardía del trasplante renal. Este estudio retrospectivo informa la frecuencia y las consecuencias de la interrupción del tratamiento en un centro en Venezuela. Se entrevistaron 303 pacientes (181 de ellos del sexo masculino) que tenían un seguimiento de más de un año después del trasplante renal y se evaluaron sus historias clínicas. Ciento veinticuatro pacientes informaron haber interrumpido el tratamiento por más de 1 semana; en 107 (86,3%) casos el motivo fue no disponer de los medicamentos inmunosupresores en la institución (incumplimiento institucional) y el resto se debió a incumplimientos voluntarios. Los episodios de rechazo agudo fueron cerca de tres veces más frecuente en los incumplidores voluntarios que en los incumplidores institucionales, probablemente porque el incumplimiento voluntario duró más ($42,7 \pm 14,1$ días [desviación estándar]) que el institucional ($18,5 \pm 11,2$ días; $P < 0,001$). La pérdida del trasplante ocurrió en 63,6% (7/11) de los incumplimientos voluntarios y en 33,3% (10/30) de los incumplimientos institucionales. El incumplimiento institucional es una causa evitable de pérdida del órgano trasplantado en algunos programas de trasplante en países en desarrollo.

Palabras clave

Inmunosupresión, negativa del paciente al tratamiento, trasplante.