Gastrointestinal Complications in Renal Transplant Recipients: MITOS Study

S. Gil-Vernet, A. Amado, F. Ortega, A. Alarcón, G. Bernal, L. Capdevila, J.F. Crespo, J.M. Cruzado, E. De Bonis, N. Esforzado, A.M. Fernandez, A. Franco, L. Hortal, and C. Jiménez, for the MITOS Study Group

ABSTRACT

Introduction and Methods. An epidemiologic multicenter study was performed to evaluate the prevalence and management of gastrointestinal (GI) complications in solid organ transplant patients. A total of 1788 recipients were included, 1132 of which corresponded to renal transplanted patients.

Results. The mean age for the renal transplanted patients was 52 ± 13.2 years. The mean time from the transplantation was 5.4 ± 5.4 years. 17.7% showed some pretransplant GI disease, while 53% presented this type of complication in the posttransplant period. Diarrhea was the most prevalent GI complication (51.5%) and digestive perforation was the GI disorder that affected the patients daily living the most. From the patients with GI complications, 71% received pharmacological treatment, using gastric protectors in 91.3% of the cases. Regarding immunosuppressive drugs, in 30.9% of the cases the dose of the drug was reduced, in 9.3% discontinued temporarily and in 7.5% discontinued permanently. These changes mainly affected the MMF (89%, 83% and 74% for dose change, temporary and permanent discontinuation, respectively).

Conclusions. The prevalence of GI complications in renal transplant exceeded 50%, and affected patients' daily living. The management of these complications was based on treatment with gastric protectors, dose reduction and/or partial or definitive MMF discontinuation.

RENAL transplantation is the most effective procedure to treat patients with chronic renal insufficiency and its results have improved with the arrival of new immunosuppressants to the therapeutic arsenal. Therefore, acute rejection rates, one of the most important factors reducing the long-term graft survival, have significantly decreased.[1]

One undesirable effect of the immunosuppressive therapy is toxicity. Thus, good management to ensure a correct balance between efficacy and safety, is critical both, increasing patients' quality of life (QoL) and graft and patient survival.

Among the most prevalent adverse events in transplant patients are the gastrointestinal (GI) complications. These complications can not only affect to the QoL of the patients (ie, nausea or diarrhea) but also have life-threatening outcomes, as digestive bleeding or perforation.[2–5] The harmful impact of these complications significantly influence the outcomes of transplantation, with a correlation between GI complications and renal transplant patient long-term survival.[3]

The origin of GI events can be multiple, and it is not easy to distinguish those related to the use of immunosuppres-

From the H. Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain (S.G.-V., J.M.C.); Hospital 12 de Octubre, Madrid, Spain (A.Am.); H. Central de Asturias, Oviedo, Spain (F.O.); H. U. Son Dureta, Palma de Mallorca, Spain (A.Al.); H. Virgen del Rocío, Sevilla, Spain (G.B.); H. Vall d'Hebron, Barcelona, Spain (L.C.); H. Doctor Peset, Valencia, Spain (J.F.C.); H. U. de Canarias, La Laguna, Spain (E.D.); H. Clínic Barcelona, Spain (N.E.); H. Dr. Negrín, Las Palmas de Gran Canaria, Spain (A.M.F., L.H.); Hospital de Alicante, Alicante, Spain (A.F.); and Hospital Gral La Paz, Madrid, Spain (C.J.).

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Address reprint requests to Dr Salvador Gil-Vernet, Hospital de Bellvitge, Nephrology Service, Feixa Llarga s/n, L'Hospitalet de Llobregat, Barcelona, Spain. E-mail: sgilvernet@csub.scs.es

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Table 1. Initial and Current Immunosuppressive Treatments

Immunosuppressive Treatment	Initial (%)	Maintenance (%)
MMF + CsA ± steroids ± antibodies	21.1	18.1
MMF + TAC ± steroids ± antibodies	42	35.5
EC-MPS + CsA ± steroids ± antibodies	1.2	2.6
EC-MPS + TAC ± steroids ± antibodies	0.3	3.6
SRL in different regimens	4.4	8.7
AZA in different regimens	17.7	7.2
Other regimens	13.1	23.7
Total No.	1132	1132

sant drugs or from other causes, such as infections.[6–8] Management of GI toxicity includes different lines of attack, the most common being the use of prophylactic drugs, such as gastric protectors and/or anti-infections therapies, the performance of diagnostic procedures to identify the cause of the complication, and the modification of immunosuppression. Regarding to the last approach, changes in immunosuppressant drugs take advantage of different safety profiles, while other regimes maintain the same drug combination. But either decrease the total dose, or increase the intakes by keeping the same daily dose (to decrease the maximum concentration of the drug). Other usual measures are temporary or permanent drugs withdrawals.

All approaches involving changes in the immunosuppressive regimens can affect their efficacy and safety, potentially increasing the risk of acute rejections and affecting graft survival.[4,5]

In the light of the impact that GI complications have in the progress of transplant patients, and scarce information that existed in Spain regarding this issue, a study with the objective to know the prevalence, impact and handling of these complications in the transplanted population was designed: the MITOS study.

The MITOS study is a large epidemiological research, carried out in recipients of renal, liver, heart and lung transplantation. It focuses on GI prevalence in the transplant population, its effect on quality of life, and how they are managed by the physicians. In this manuscript, we are presenting the results of the renal subpopulation.

MATERIALS AND METHODS

The MITOS solid organ transplant study enrolled 1788 patients in a epidemiologic cross-sectional research carried out by 151 investigators in Spanish transplant units, and was approved by Hospital of Bellvitge Ethic Committee. We present the results of the widest sub-study, which involved 1132 patients who underwent a kidney transplant.

The goal was to calculate the prevalence of the GI complications in renal transplant patients and to asses the main correlated variables. Results for this type of organ can be thereafter compared with those from liver, heart and lung recipients participating in the same study.

Patients were 18 years old or older, solid organ transplant recipients, had a functioning graft and were taken maintenance immunosuppressive drugs. Data were collected from the patients visiting the site and from their prior medical records. Descriptive statistics of the variables analyzed were presented with the absolute and the relative frequencies of qualitative variables. Mann-Whitney or *t*-tests were used to compare the independent samples and Wilcoxon or *t*-test for the related samples. Test Chi-square was used for the discrete variables. Descriptive and inferential analyses of the data were performed with the SPSS program, version 13.0.

RESULTS

Demographics showed predominately male recipients 62.3%, with a mean age of 52 ± 13.2 years, who mostly were in need of a kidney after suffering glomerulonephritis (28.1%), and that had been transplanted for an average of 5.4 ± 5.4 years. Rejections occurred in 22.3% of the patients, and 96.8% of the kidneys came from deceased donors. Recipient serology was positive for CMV in 78.3%, HCV in 9.4%, HBV in 3.0% and HIV in 0.3% of all patients. Following the present trend in the administration of CNI (calcineurin inhibitors), the initial and current immunosuppressive treatments (Table 1) showed a more frequent addition of Tacrolimus than of CsA in the MMF ± steroid + antibody combination (42.0% and 35.5% vs. 21.1% and 18.1%), with little differences between the early prescribe and the maintenance medication, except for the decay of the Azatioprine in different regimes. Shifts between initial and maintenance drugs increased immunosuppressant doses from an average 1701.4 ± 447.1 mg/d to 1134.8 ± 458.2 mg/d for MMF, and a similar rise occurred from an average 1487.4 ± 268 mg/d to 1547.2 ± 1054.3 mg/d for EC-MPS.

Patients presented 17.7% pre- and 53.0% posttransplant GI complications, the later listed in Table 2. Although diarrhea (51.5%) showed higher frequency, digestive perforation was the most disrupting. More men than women suffered from GI complications, 59.8% vs. 40.2% (P = .066), and a higher percentage of patients (48.3%) presented one GI complication rather than two or more. The prevalence of diarrhoea was 58% for the patients on treatment with MMF + TAC vs. 47% on MMF + CsA.

Seventy-one percent of patients needed pharmacological treatment, mostly gastric protectors (91.3%), and in 15.5% of the patients measures were taken at diagnostic proce-

Table 2. Impact of GI Complications on Daily Activities

Patients With GI Complications (n = 600; 53%)	GI Complications		Affected Daily Activities (%)
	n	%	
Diarrhea	309	51.50	53.72
Heartburn or dyspepsia	239	39.83	36.61
Abdominal pain	153	25.50	58.16
Nausea	145	24.17	48.48
Vomiting	124	20.67	60.00
Constipation	121	20.17	26.36
Reflux	75	12.50	28.79
Anorexia	61	10.17	56.00
Digestive bleeding	36	6.00	60.00
Digestive perforation	6	1.00	66.67

Table 3. Variables Related to GI Complications

	GI Complications		
	Yes	No	*P*
Male (%)	59.8	65.2	.066
Time since transplantation (y)	5.7	5.1	<.05
Graft rejection episodes (%)	21.8	22.9	.658
Hospital readmissions (%)	69.2	52	<.001
Mean creatinine (mg/dL)	1.8	1.6	<.001
Mean hemoglobin (g/dL)	12.9	13.3	<.001
Mean leukocytes ($\times 10^6$ L)	7036	7576	<.001

dures. Management also involved reducing immunosuppressant treatment dose (30.9%, with 89% lowering MMF), treatment interruption (9.3%, with 83% stopping MMF), and treatment discontinuation (7.5%, with 74% withdrawing MMF).

Most interestingly, this study shows a series of variables related to the GI complications (Table 3). Thus, in the group that suffered GI complications, the time since transplantation was longer, 5.7 vs. 5.1 years ($P < .05$). In addition, more patients underwent GI disorders in the tacrolimus than in the CsA group (50.2% vs 40.2%). Patients with GI complications showed more hospital admissions. Finally, lower hemoglobin and leukocyte values and higher creatinine levels were also estimated as related to the GI complications ($P < .001$).

DISCUSSION

The present sub-study has confirmed previous reports showing a high prevalence of GI complications in the transplant population.[3,8] Specifically, in our analysis, 53% of the recipients suffered from this disorder, with diarrhea occuring at a higher rate, and exceeding that of the total solid organ population of the MITOS study (51.5 vs. 24.7%). Furthermore, the prevalence of diarrhea was higher in the patients under treatment with MMF + FK than in those receiving MMF + CsA (58 vs. 47%).

Two large trials involving tacrolimus in renal transplant patients also revealed increased rates of tacrolimus associated diarrhoea, and a substantial difference in the results when compared with CsA.[9,10] Another study,[11] focussed specifically on diarrhea following renal transplantation, reported that the most frequent causes for diarrhoeal episodes were infectious agents and drugs. As for this sub-study, other GI disorders included abdominal pain, heartburn/dyspepsia and bleeding and a lower rate of nausea, reflux and anorexia; all with higher rates than those showed by the solid organ transplant population in the general study. The incidence recorded regarding vomiting, constipation and intestinal perforation was the same for both the sub-study and the general population.

Dose reduction, interruption or discontinuation of certain immunosuppressive drugs, such MMF or tacrolimus, is an important strategy to manage GI toxicities, particularly diarrhea in transplant patients.[6] Several studies have reported that MMF dose reduction and discontinuation after GI complications are associated with increased risk of renal transplant graft failure.[4,8,12,13] In our study GI complications affected patients' daily living in about 50% of the cases, and had a negative impact over the hemoglobin, leukocyte and creatinine analytical parameters. We have also recorded MMF dose reduction to manage side effects. In fact, 89% of the changes in the immunosuppressive treatment consisted in the reduction or interruption of MMF. Similarly to a retrospective analysis,[7] one-third of adult kidney recipients who received MMF after the transplant suffered GI complications during the first year after the transplant. More than 21% of the patients with GI complications suspended the treatment, as compared with

Table 4. Multicenter Study in Spain

Participant Centers	Included Patients
Clínica Puerta de Hierro	20
Clínica Universitaria de Navarra	12
Complejo H. Ntra. Sra. De Alarcos	14
Fundación Jiménez Díaz	14
Fundación Pulgvert	51
H. Central de Asturias	30
H. Clínic	49
H. Clínico de Santiago	15
H. Clínico de Valladolid	14
H. Clínico San Carlos	15
H. de Bellvitge	56
H. de Canarias	20
H. De Cruces	27
H. De Galdakao	15
H. de Txagorritxu	14
H. De Valdecilla	43
H. Del Mar	23
H. Donostia	15
H. Dr. Negrín General de Canaria	30
H. Dr. Pesset	30
H. General de Albacete	15
H. General de ALicante	30
H. Germans Trias I Pujol	30
H. Gregorio Marañón	15
H. Insular de Canaria	12
H. Juan Canalejo	51
H. La Fe de Valencia	29
H. La Paz	58
H. Miguel Servet	60
H. Ntra. Sra. de la Candelaria	21
H. Nuestra Sra. Del Cristal	5
H. Provincial de Pontevendra	6
H. Puerta del Mar de Cádiz	53
H. Ramón y Cajal	27
H. Reína Sofía	15
H. San Millán	14
H. Santiago Apóstol	17
H. Son Dureta	15
H. Vall d'Hebrón	22
H. Virgen de la Arrixaca	45
H. Virgen del Rocío	70
H. Xeral de Lugo	15
Total No.	1132

16% that did not have any GI complications. This study also revealed how the presence of GI complications significantly reduced graft survival to 4 years.

As opposed to MMF, in our study the EC-MPS dose was increased from the initial to the maintenance dose. Our research has shown that a reduction of EC-MPS was not used as a strategy to manage GI side effects. Other reports have reported a comparable efficacy and safety profile of EC-MPS to MMF.[14–16] Furthermore, these studies have confirmed that maintenance patients can be safely converted from MMF to EC-MPS, without compromising efficacy or safety. A 12-month pivotal study which investigated whether stable renal patients could be converted from MMF to EC-MPS therapy, without compromising safety and efficacy, showed similar incidence of GI complications at 3 and 6 months. However, there was a trend toward reduced severity of GI side effects with EC-MPS at 12 months, with significantly fewer serious infections and lower 12 month efficacy failure rates (EC-MPS 7.5% vs 12.3% MMF).[16]

In a recent study, where efficacy and safety of converting stable renal transplant patients from MMF to a bioequivalent dose of EC-MPS was evaluated, GI adverse events occurred in 23.5% of the patients and the rate of dose adjustments as a result of a GI adverse event was very low (2.2%).[17]

Therefore, from this and other studies, we propose that the conversion of MMF to EC-MPS provides doctors with a valid therapy alternative for the immunosuppression.

CONCLUSION

The prevalence of GI complications reached 53% and diarrhea was the most frequent GI complication. In more than half of the cases, these complications did indeed affect patients' daily activities. Thus, patients with GI complications showed more hospital admissions. Significant variables correlated to these disorders were lower hemoglobin values and worst graft function measured by serum creatinine levels. Shifts in the immunosuppressive treatment consisted mainly in the reduction or interruption of MMF (89%).

This study adds a new insight to the strategies needed to effectively treat GI complications, avoiding the potential negative effects of immunosuppressive adjustments/discontinuations. (Table 4).

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