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ORIGINAL ARTICLE

Gastrointestinal symptoms impair quality of life in Italian renal transplant recipients but are under-recognized by physicians

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Summary

We assessed patient- and physician-reported prevalence of gastrointestinal symptoms and their impact on quality of life (QOL) in Italian renal transplant recipients with stable graft function. Patients ≥18 years with a renal allograft functioning for ≥6 months and stable serum creatinine levels of <2.5 mg/dl were enrolled. Physicians and patients completed an Italian translation of the Gastrointestinal Symptom Rating Scale (GSRS) and Gastrointestinal Quality of Life Index (GIQLI) questionnaires. The average time since transplantation ($n = 1130$) was 5.9 years. Forty-two immunosuppressant drug regimens were reported. The top three regimens (cyclosporine/mycophenolate mofetil/steroids; tacrolimus/mycophenolate mofetil/steroids; cyclosporine/steroids) accounted for approximately 40% of patients. In the physician interview, 39.2% of patients had ≥1 gastrointestinal symptom vs. 88.3% of patients in the self-administered questionnaire. The prevalence of GSRS symptoms was similar for each of the most frequently prescribed immunosuppressant drug regimens. GIQLI total score was significantly poorer in patients with versus those without gastrointestinal symptoms (121.8 ± 17.6 vs. 138.4 ± 3.7; $P < 0.0001$), and there was a strong inverse correlation between GIQLI and patient-reported GSRS scores (Pearson's correlation coefficient −0.816; $P < 0.0001$). Gastrointestinal symptoms are frequent in renal transplant patients, are under-evaluated by physicians and may adversely impact on patient QOL.

Introduction

Although transplantation may not restore 'normal' life to the patient, a review of the literature showed that there are distinct quality of life (QOL) benefits of transplantation [1], particularly compared with dialysis [2,3]. On the other hand, medicalization, fear, gratitude, and coping with self-care to maintain the kidney's health pervade the lives of the recipients, and these psychosocial effects of transplantation are long-lasting [4]. In this setting, the impact of gastrointestinal symptoms on the QOL of renal transplant recipients has been poorly investigated.

Gastrointestinal complications are frequent in renal transplant recipients and may involve any segment of the gastrointestinal tract [5,6]. These disorders may be related to stress, infections and/or exacerbation of pre-existing gastrointestinal pathology. In addition, immunosuppressive agents may cause gastrointestinal side effects either directly or by favouring the development of bacterial and/or viral infection [5–7]. In about 10% of renal transplant

patients, severe gastrointestinal disorders may develop eventually leading to graft loss and even patient death [7]. Gastrointestinal complications may also result in immunosuppressant drug dose reductions and associated risk of organ rejection [8–10]. However, many gastrointestinal symptoms are trivial and are often not referred by the patient to the physician. Nevertheless, even minor gastrointestinal symptoms may impair QOL in renal transplant recipients [11,12], and may threaten long-term transplant stability through reduced adherence to immunosuppressant therapy [13].

Recently, Kleinman *et al.* [12] validated the use of the Gastrointestinal Symptom Rating Scale (GSRS) and the Gastrointestinal Quality of Life Index (GIQLI) as specific instruments to assess the presence and severity of gastrointestinal symptoms and their impact on QOL in renal transplant recipients. By using the GSRS, Ekberg *et al.* [11] reported a high prevalence of gastrointestinal symptoms in Scandinavian renal transplant recipients in an observational survey based on postal questionnaires, and demonstrated that gastrointestinal symptoms were associated with impaired QOL. On the other hand, physicians underestimated gastrointestinal symptoms and overestimated QOL in their renal transplant patients [14].

The main objective of the Complications related to gastroEnteric symptoms in renal TRAnsplant patients (CETRA) study was to evaluate the prevalence of gastrointestinal symptoms in patients with stable renal transplant and without underlying diseases that could cause gastrointestinal symptoms. We assessed the prevalence of gastrointestinal symptoms and their impact on QOL in a large cohort of Italian renal transplant recipients with stable graft function in a prospective observational manner. Self-administered GSRS was used to assess the baseline presence and severity of gastrointestinal symptoms and the results were compared with those obtained by a physician interview. The relationship between gastrointestinal symptoms and ongoing treatments as well as the impact on gastrointestinal symptoms on QOL measured with the GIQLI were also investigated.

Materials and methods

Patients

This multicenter study involved 23 Italian transplant centers. Renal transplant recipients of either gender, who were aged 18 years or more, with their allograft functioning for at least 6 months were eligible for the study. Other inclusion criteria were serum creatinine level <2.5 mg/dl with variation of less than 30% between two consecutive measurements. Key exclusion criteria were as follows: participation in other investigational studies; medical or surgical complications at risk of hospitalization; a history of severe gastrointestinal complications before transplantation; severe psychiatric disease; chronic active viral hepatitis; concomitant severe medical or surgical complications. A total of 1136 transplant patients were screened and 1130 patients meeting the inclusion/exclusion criteria were enrolled.

The study was approved by the ethics committees of the participating transplant centers and all patients provided informed consent.

Study design

This was an observational prospective study. Aims of this study were to assess the prevalence of gastrointestinal symptoms and their impact on QOL of renal transplant recipients. We admitted only patients with stable serum creatinine <2.5 mg/dl and free of other diseases. We realize that these criteria do not reflect the whole transplant population seen in clinical practice but we deliberately wanted to avoid any interference of renal failure or other concomitant complications to better know the impact of gastrointestinal symptoms in patients with stable renal allograft function and without other complications. For the same reason we did not investigate the frequency and severity of other adverse events caused by the different immunosuppressive regimens used. We considered that a number of 1000 patients meeting the inclusion criteria were sufficient to meet our goals. The recruitment was good and we stopped the enrollment after 1130 patients were accepted.

Patient demographic data and details of prescribed treatment (immunosuppressant and other drugs), as well as main clinical and laboratory data, were collected at the baseline visit.

Gastrointestinal symptoms were assessed by patients and physicians using the GSRS [15]. This scale, consisting of 15 questions, was developed to assess the pattern and severity of gastrointestinal symptoms across five domains (abdominal pain, reflux syndrome, diarrhea, indigestion syndrome and constipation) and has been used to differentiate renal transplantation patients with and without gastrointestinal symptoms [12]. An Italian language translation of this scale has been validated in patients with gastroesophageal reflux disease [16]. Physicians recorded the presence or absence of symptoms occurring in the last week before the visit according to a simple yes or no response from patients. In the self-administered questionnaire, patients assigned a score for the level of discomfort for each symptom ranging from 1 to 7 (1 = no discomfort, 2 = minor, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = very severe discomfort). When dichotomized, 'no bothersome symptoms' ('1') is considered as denying the symptom, while scores 2–7 are

considered as affirming the symptom [17]. A mean score across the 15 questions in the five domains was calculated for each patient. Patients were asked to complete the GSRS questionnaire at baseline and at 3, 6 and 12 months of follow-up.

The GIQLI was used to assess the impact of gastrointestinal symptoms on the QOL [18]. This index includes 36 items grouped in five domains: gastrointestinal symptoms, emotion, physical function, social function, and medical treatment. Patients scored each item on a scale of 0–4. A higher score indicated better QOL. Patients were required to complete the questionnaires at the scheduled visits 3 months (visit 2), 6 months (visit 3), and 12 months (visit 4) after the baseline visit.

Statistical analysis

Data are presented as mean ± SD. The Student t test and Wilcoxon test were used to compare continuous variables. Fisher and Chi-square tests were used to compare frequency values. Predictors of gastrointestinal symptoms categorized as GSRS scores in the ≥75th percentile versus GSRS scores in the ≤25th percentile were calculated initially by univariate analysis and then using multiple logistic regression, including treatment, gender, age and the length of time since transplantation as variables in the model. Odds ratios (OR) were adjusted for the variables included in the final model.

Results

Patient demographics and treatment

A total of 1130 patients were enrolled in the study and their demographic and clinical data are provided in Table 1. The mean time since transplant was 5.9 ± 5.4 years and the clinical state of patients was generally good. Graft function was adequate, with a mean creatinine clearance of 60.1 ± 21.0 ml/min Table 1. Hemoglobin levels were within the normal range, and mean systolic and diastolic blood pressure levels were within normal values, although most patients (72.8%) required antihypertensive medication.

The most frequently prescribed immunosuppressive agents were steroids (72%), cyclosporine (51%), mofetil mycophenolate (46%) and tacrolimus (28%). About 10% of patients were given azathioprine, another 10% sirolimus, 8% enteric-coated mycophenolic acid and 2% everolimus. Forty-two different immunosuppressant drug regimens (monotherapy or combination therapy) were reported among patients at the time of inclusion in the study. The combinations of cyclosporine or tacrolimus plus mycophenolate mofetil (MMF) and steroids, and cyclosporine plus steroids were the three most commonly prescribed regimens, accounting for 15.6%, 13.5%, and 9.6% of patients, respectively. Overall, 495 patients received MMF as part of their immunosuppressive regimen, most of whom received a dosage between 0.5 and 2.0 g/day (Fig. 1).

Many patients also received concomitant non-immunosuppressant medications including antacids (654 patients), statins (384 patients), vitamin D (169 patients), insulin (50 patients) and oral hypoglycemic agents (39 patients). On average, each patient was taking 11 ± 4 tablets/capsules per day, comprising 6 ± 2 immunosuppressant tablets/capsules and 5 ± 3 nonimmunosuppressant tablets/capsules.

Gastrointestinal symptoms

Overall, patients were more likely to report gastrointestinal symptoms than physicians. Thus, the number of

Table 1. Patient demographics and clinical characteristics.

Characteristic	*n* = 1130
Age (years)	29.2 ± 12.0
Male gender	63.5%
Weight (kg)	69.4 ± 13.7
Time on dialysis prior to transplant (years)	3.5 ± 3.5
Time since transplant (years)	5.9 ± 5.4
Deceased donor	89.7%
Serum creatinine (mg/dl)	1.5 ± 0.4
Creatinine clearance (ml/min)	60.1 ± 21.0
Serum blood urea nitrogen (mg/dl)	57.7 ± 27.6
Serum albumin (mg/dl)	4.3 ± 0.4
Serum glucose (mg/dl)	95.2 ± 25.7
Hemoglobin (g/dl)	13.1 ± 1.6
Systolic/diastolic blood pressure (mmHg)	131.4 ± 14.3/80.2 ± 9.9

Continuous variables are reported as mean ± standard deviation.

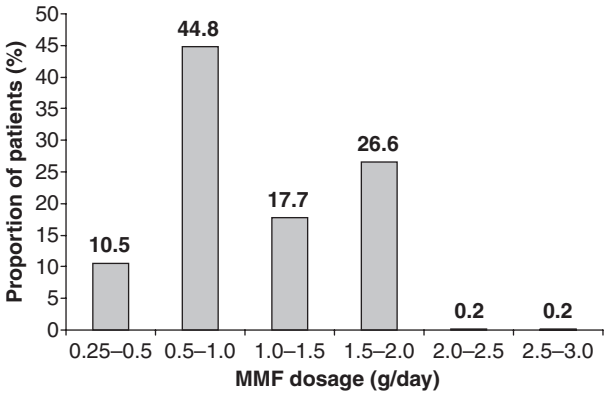

Figure 1 Mycophenolate mofetil (MMF) dose among patients receiving MMF.

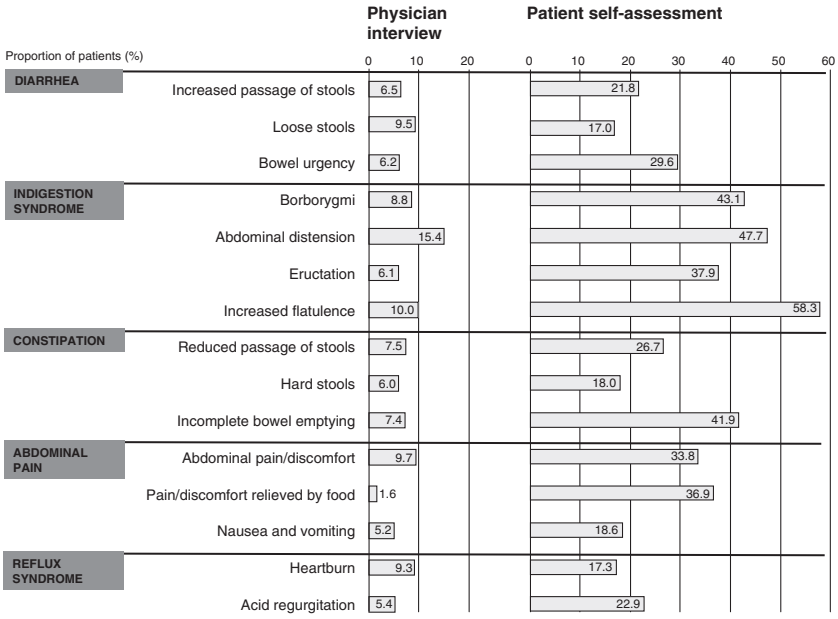

Figure 2 Prevalence of gastrointestinal symptoms as reported by patient or physician.

patients reporting at least one gastrointestinal symptom (defined as a score of >1) was 88.3% whereas physicians scored only 39.2% of patients as having at least one symptom. When considering individual GSRS symptoms across all five domains, patients reported a higher incidence than physicians in every case, ranging from approximately twofold higher (heartburn, loose stools) to sixfold higher (eructation, flatulence) (Fig. 2). The four symptoms most frequently reported by patients were, in order of prevalent, flatulence, abdominal distension, borborygmi and the sensation of incomplete bowel emptying. By contrast, physicians reported the presence of abdominal distension, flatulence, abdominal pain/discomfort and loose stools most often (Fig. 2).

The baseline prevalence and severity of individual upper and lower gastrointestinal symptoms reported by patients are shown in (Fig. 3). The mean patient-reported GSRS total score was 1.53 ± 0.51. Combining individual symptoms into the five domains of the GSRS gave scores of 1.31 ± 0.61 for reflux syndrome, 1.44 ± 0.88 for diarrhea syndrome, 1.49 ± 0.72 for constipation syndrome, 1.49 ± 0.67 for pain syndrome and 1.77 ± 0.79 for bloating syndrome. Follow-up over the course of 12 months showed that the prevalence and severity of gastrointestinal symptoms were stable (Fig. 4). The proportion of patients with at least one symptom that they rated as moderate-severe (GSRS score of 4–7) was 37.0%. In 228 of 443 cases of gastrointestinal symptoms recorded by the physician,

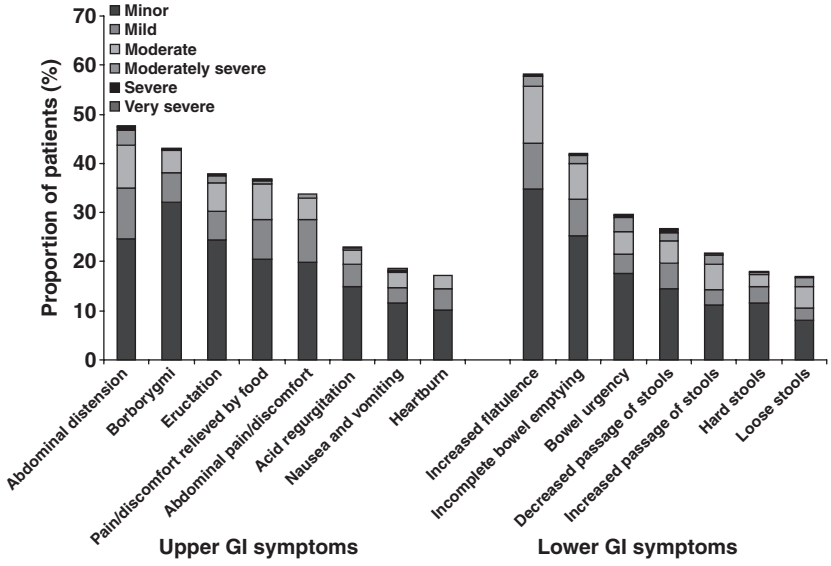

Figure 3 Prevalence and severity of individual gastrointestinal (GI) symptoms reported by patients. Severity was assessed using the Gastrointestinal Symptom Rating Scale (1 = no discomfort, 2 = minor, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = very severe discomfort).

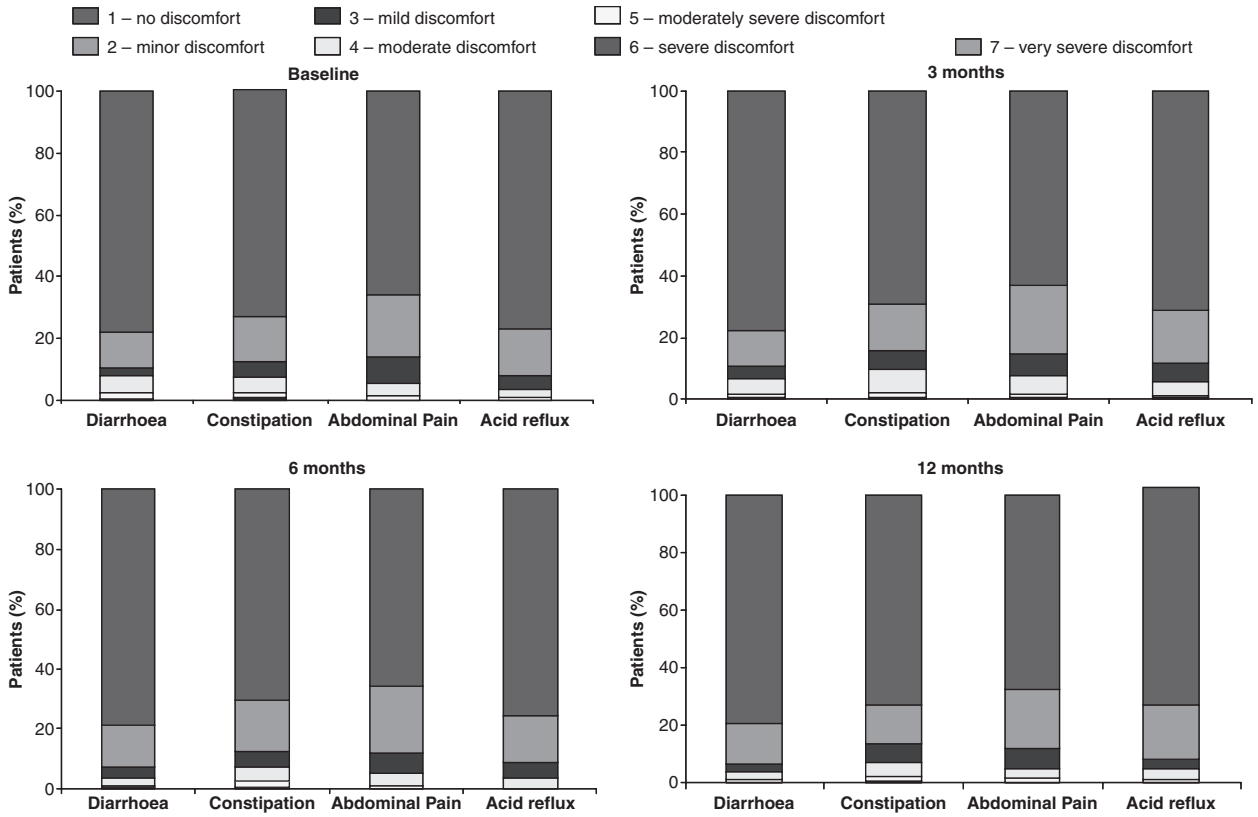

Figure 4 Prevalence and severity of diarrhea, constipation, abdominal pain and acid reflux reported by patients at baseline and at 3, 6 and 12 months of follow-up. Severity was assessed according to the Gastrointestinal Symptom Rating Scale (1 = no discomfort, 2 = minor, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = very severe discomfort).

symptoms were attributed to immunosuppressive therapy (20.1% of total population), and after the baseline visit, clinicians prescribed drugs to relieve gastrointestinal symptoms in 298 (26.4%) of patients.

The patient-reported prevalence of each GSRS symptom was similar for each of the six most frequently prescribed immunosuppressant drug regimens, including three regimens incorporating MMF. A direct comparison of the prevalence of patient-reported gastrointestinal symptoms among patients receiving regimens with or without MMF did not reveal any differences (data not shown). Similarly, although the prevalence of physician-recorded gastrointestinal symptoms was lower, there were no clear differences in the prevalence of these symptoms among patients receiving regimens with or without MMF (data not shown).

Quality of life

Quality of life was significantly worse in patients with gastrointestinal symptoms than in patients without, whether symptoms were reported by patient or doctor. Patients ($n = 997$) who reported at least one gastrointestinal symptom (GSRS score >1) had a significantly lower GIQLI total score than those ($n = 133$) who did not report any gastrointestinal symptoms (121.8 ± 17.6 vs. 138.4 ± 3.7; $P < 0.0001$). All five domains of the GIQLI were significantly impaired by the presence of gastrointestinal symptoms ($P < 0.0001$; data not shown). Among those patients with at least one symptom with a severity score of ≥4 ($n = 349$), the GIQLI total score was further impaired (109.9 ± 18.8). The impact of moderate-to-severe gastrointestinal symptoms on QOL was particularly evident for emotional and physical function domains of the GIQLI (Fig. 5). There was a strong inverse correlation between the total GIQLI score and the patient-reported GSRS score (Pearson correlation coefficient −0.816; $P < 0.0001$).

When physicians recorded gastrointestinal symptoms as present ($n = 385$) or absent ($n = 566$), GIQLI total scores were also significantly lower in patients with symptoms (115 ± 19.4 vs. 128.7 ± 14.6; $P = 0.0001$) as were each of the five domain scores (all $P < 0.0001$; data not shown).

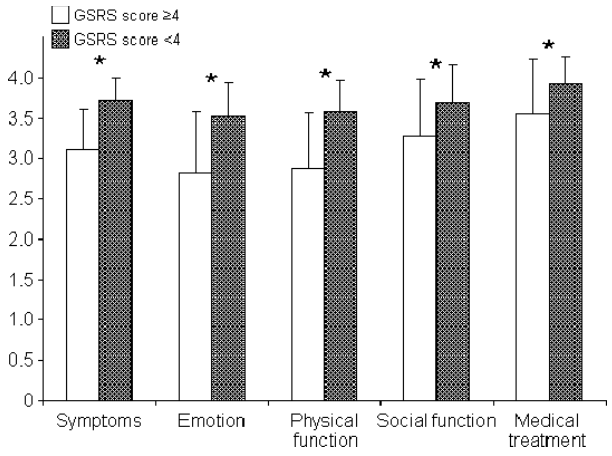

Figure 5 Patient-reported domain scores for Gastrointestinal Quality of Life Index for patients with moderate-severe gastrointestinal symptoms [Gastrointestinal Symptom Rating Scale (GSRS) score ≥ 4] and those with no symptoms or mild symptoms only (GSRS score < 4). *Statistically significant difference ($P < 0.0001$).

All 15 of the GSRS gastrointestinal symptoms appeared to influence QOL. Thus, the presence of any of the gastrointestinal symptoms, whether patient- or physician-reported, was associated with a statistically significantly lower GIQLI score than was seen in patients without that symptom ($P < 0.005$; data not shown).

Finally, there were no obvious differences in GIQLI scores among patients receiving different immunosuppressant therapy. The total GIQLI scores ranged from 118.0 ± 21.6 for tacrolimus + steroids to 126.5 ± 14.0 for cyclosporine + MMF + steroids, out of a total possible score of 144.

Discussion

This study involving over one thousand patients has shown that gastrointestinal symptoms occur in almost 90% of stable renal transplant patients and have a significant impact on patients' QOL. Only around 40% of patients reported one or more gastrointestinal symptom when interviewed by their physician. Our data also indicate that physicians significantly underestimate the occurrence of gastrointestinal problems in their patients, a discrepancy already reported previously in a range of other diseases, including gastroesophageal reflux disease [19]. We could not find any significant association between the presence of gastrointestinal symptoms and a specific immunosuppressant drug or drug combination.

The impact of gastrointestinal symptoms on QOL in renal transplant recipients was presented recently by Ekberg *et al.* [11] and while there are some similarities between their study and ours, a number of important differences exist. Both of these studies were large observational cohort studies, evaluated the prevalence and impact of gastrointestinal symptoms on QOL in stable renal transplant patients and used GSRS to assess gastrointestinal symptoms. However, Ekberg *et al.* [11] conducted telephone and postal questionnaires across a number of Scandinavian countries to determine a point prevalence of gastrointestinal symptoms. A later publication detailed the nephrologist's perception of these symptoms [14], but the responses to the patient and physician questionnaires were anonymous and could not be compared. In the current study, we examined a population from Southern Europe, examined QOL at a number of time points over the 1-year study period and concurrently obtained data from physicians on gastrointestinal symptoms.

A high prevalence of gastrointestinal symptoms was seen in renal transplant recipients in our study, with almost 90% of patients reporting at least one gastrointestinal symptom, and this is comparable with the incidence of 92% reported in the study by Ekberg *et al.* [11]. Interestingly, the proportion of patients reporting individual complaints, as shown in (Fig. 2), was significantly lower than that reported in the Scandinavian study [11]. For example, the incidence of indigestion, abdominal pain and constipation reported by Ekberg *et al.* [11] was 83%, 69%, and 58%, respectively and was markedly higher than that in our study. The reason for this is unclear, but it may reflect the differences in patient demographics. While both studies enrolled a similar proportion of males and females, patients in our study were substantially younger, and closer to receipt of transplant than those enrolled in the Scandinavian study. The difference in age might partly accounts for the discrepancy between the Italian and Swedish populations, as it has been demonstrated that the QOL is better in younger renal transplant recipients [20]. Moreover, the darker climate may have also favoured a higher incidence of depression and a poorer QOL in the Swedish patients [21,22]. The two Scandinavian surveys dramatically highlighted this discrepancy among nephrologists and renal transplant recipients, where nephrologists estimated that as few as 20% of their patients experienced gastrointestinal problems compared with a patient-reported prevalence of 92% using the GSRS questionnaire [11,14].

Physicians also tended to underestimate the impact of these problems on their patients' QOL [11,14]. In this study, the prevalence of symptoms considered by the patient to be moderate-to-severe was 37%, closer to the overall physician-rated prevalence. It is possible that the physician did not consider mild symptoms or symptoms of an ostensibly more trivial nature (for example borborygmi, eructation), or that patients underestimated the importance of some symptoms and did not report

them at the time of clinical evaluation. Although physician and patient attention may be rightly focussed on graft function and major complications, such as hypertension, diabetes and infection, the presence of other symptoms may be indicative of a progressive or potentially serious gastrointestinal complication [23].

Notwithstanding these issues, the presence of gastrointestinal symptoms was associated with a significant reduction in patient QOL, and this was true for all 15 symptoms assessed by the GSRS questionnaire. This is in agreement with the study by Ekberg *et al.* [11] which used the Short-Form 36 to measure QOL. While the theoretical maximum GIQLI score is 144, the mean score in our patients with symptoms was 115, exactly the same mean value of 115 (range 70–140) reported by Italian patients 49 months after laparoscopic myotomy for esophageal achalasia [24].

Nonadherence to immunosuppressants is a major cause of renal transplant failure [25] and is frequently underestimated by the physician [26]. Impaired QOL may contribute to a patient's poor compliance with their treatment regimen, a possibility perhaps enhanced by the large number of tablets and/or capsules each patient may have to take. In this study, the mean number of tablets/capsules per day required by patients with stable renal allograft function was 11 ± 4, and almost 50% of this total comprised non-immunosuppressant drugs, many of which were prescribed to manage gastrointestinal side effects (physicians prescribed medication for gastrointestinal symptoms for a quarter of patients, and 58% of patients took antacids). If patients do not effectively communicate the burden of illness they suffer, even if seemingly trivial, then physicians will not have all the information they need to make treatment changes that lead to improved QOL. In the study by Ekberg *et al.* [14], almost all nephrologists expected their patients to raise gastrointestinal problems with them and only 52% reported that they routinely asked their renal transplant patient about gastrointestinal symptoms. The use of a patient questionnaire such as the GSRS may provide a basis for subsequent, full discussion of symptoms in consultation with the physician, an approach that has proven useful [27,28].

There was a large range of treatment regimens used in this study of stable transplant patients, although some 40% of patients were prescribed one of three combinations. This study and the trial by Ekberg *et al.* [11] showed that corticosteroids, cyclosporine, MMF, tacrolimus and azathioprine were the most commonly taken immunosuppressive medications by the patient. When we analyzed the symptom prevalence or QOL according to the immunosuppressant drug regimen, we found no obvious differences in the tolerability of particular regimens. Ekberg *et al.* [11] found a significant association between tacrolimus and diarrhea and constipation, and between sirolimus and indigestion and abdominal pain. However, neither study showed a significant correlation between gastrointestinal symptoms and the use of MMF. This finding is consistent with our data, which showed no effect of MMF on the prevalence of patient-reported gastrointestinal symptoms. This is important as previous data have suggested a high rate of gastrointestinal symptoms with MMF [29] that may be alleviated by the conversion to enteric coated mycophenolate sodium [30]. It should be borne in mind, however, that our data are confounded by the diversity of treatment regimens. Nearly three-quarters of the patients in our study who were taking MMF as part of their immunosuppressive regimen received a dose of 1.5 g/day or lower and in half the dose was 1 g/day or lower. Thus as a group these patients were receiving relatively low MMF dosage, which may help explain the lack of effect of MMF treatment of gastrointestinal symptomatology.

It is important to underline that it is well-established that altering the dose of MMF correlates with a significantly worse clinical outcome in renal transplant recipients. MMF dose reduction or discontinuation following a gastrointestinal complication is associated with an increased risk of acute rejection and poorer long-term graft survival [8].

The patients in this study were stable, with a mean period of almost 6 years from transplant. We do not have historical data for the period after transplantation and prior to enrollment in this ongoing study. However, it is clear that treatment remains suboptimal with respect to gastrointestinal symptoms and ongoing QOL in a large proportion of patients.

In conclusion, the results of this large observational study confirm the negative impact of gastrointestinal symptoms on renal transplant patients and highlight the fact that physicians may underestimate the prevalence of gastrointestinal symptoms. Introducing the use of a patient-completed questionnaire such as the GSRS may enable the physician to get more detailed information about the burden of illness of patients on which to make appropriate treatment decisions.

Authorship

CP and DC: study organization. CP, DC and GB: study performing. CP, DC and MN: paper writing.

Conflict of interest

D. Colombo is a part-time employee at Novartis Pharma, Italy. M. Novara is an employee of Novartis Pharma, Italy. C. Ponticelli is a consultant of Novartis Pharma, Italy.

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