Transpl Int (1996) 9 [Suppl 1]: S41–S44

L. B. Hilbrands
J. Rischen-Vos
R. Hené
W. Weimar
K. Assmann
A. J. Hoitsma

Randomized trial of misoprostol in patients with chronic renal transplant rejection

L. B. Hilbrands (✉) · K. Assmann · A. J. Hoitsma
Academic Hospital St. Radboud,
G. Grooteplein 10, NL-6525 GA Nijmegen,
The Netherlands

J. Rischen-Vos · W. Weimar
Academic Hospital Dijkzigt,
Dr. Molewaterplein 40,
NL-3015 GD Rotterdam, The Netherlands

R. Hené
Academic Hospital Utrecht,
Heidelberglaan 100,
NL-3584 CX Utrecht, The Netherlands

Abstract Chronic vascular rejection is a major cause of long-term graft failure after renal transplantation. We investigated the effect of the addition of misoprostol (200 μg four times daily) to standard immunosuppressive therapy on the outcome of chronic rejection in a double-blind, placebo-controlled trial. Patients had to fulfill predefined histological and clinical criteria. After an entry of 40 patients into the study (22 misoprostol, 18 placebo), the inclusion of additional patients was terminated because of a high incidence of withdrawal due to adverse effects. Of the patients who used their study medication for at least 3 months (16 misoprostol, 15 placebo), graft function deteriorated in all but 5 misoprostol-treated and all but 2 placebo-treated patients. There was no difference in dialysis-free survival. Withdrawal because of adverse effects (mainly gastrointestinal complaints) occurred in 3 cases in the placebo group and in 11 cases in the misoprostol group ($P < 0.05$). In conclusion, we found no evidence for a beneficial effect of misoprostol on the course of chronic renal allograft rejection, while use of the drug was accompanied by a high incidence of side effects.

Key words Renal transplantation · Chronic rejection · Misoprostol

Introduction

Short-term graft survival rates after renal transplantation have significantly improved in recent decades. However, chronic rejection continues to result in a steady number of late allograft failures. When graft loss due to patient death is excluded, chronic rejection is the leading cause of late allograft loss in renal transplant patients [4, 11]. The pathophysiological mechanisms leading to chronic rejection are not clear. There is ample evidence that the immunological response plays an important role, at least in the initiation of vascular injury that ultimately results in luminal obliteration [6, 12]. In recent years, non-immunological factors such as ischemia-reperfusion injury, reduced nephron mass, cyclosporine nephrotoxicity, hypertension, and hyperlipidemia have increasingly been implicated in the course of chronic allograft dysfunction [1, 12]. Currently, there is no effective treatment for patients with chronic rejection. Misoprostol is a synthetic prostaglandin E_1 analogue with high oral bioavailability. In animal models [3, 13] and human renal transplantation [7], misoprostol has been demonstrated to possess immunosuppressive properties. In addition, misoprostol was shown to protect against ischemic and toxic renal injury [8, 9] and to improve renal allograft function [7]. On the basis of these results, we initiated a randomized prospective trial to investigate the efficacy of misoprostol for the treatment of chronic rejection in renal transplant recipients.

Table 1 Clinical characteristics of patients at entry into the study. Numerical data are given as medians with ranges (*M/F* male/female, *CsA* cyclosporine A, *Aza* azathioprine, *Pred* prednisone)

		Misoprostol ($n = 22$)	Placebo ($n = 18$)
Sex (M/F)		17/5	10/8
Age (years)		43 (26–61)	45 (18–68)
First/second graft		17/5	12/6
Time after transplantation (months)		41 (13–194)	62 (12–147)
Baseline immunosuppressive therapy:	CsA + Pred	8	5
	CsA + Aza	1	0
	CsA + Aza + Pred	3	2
	Aza + Pred	10	11
Creatinine clearance (ml/min)		34 (10–60)	30 (11–68)
Proteinuria (g/l)		1.9 (0–7.4)	2.6 (0.1–8.8)
Mean arterial pressure (mm Hg)		113 (100–143)	116 (92–147)
Number of antihypertensive drugs		2 (0–3)	2 (0–3)

Patients and methods

Patient population

Forty adult renal tansplant patients with chronic rejection were recruited from three Dutch transplantation centers between December 1991 and February 1994. Patients were eligible for this study if a graft biopsy showed the presence of arterial intimal fibrosis and/or chronic transplant glomerulopathy. All biopsies were examined by one pathologist (K. A.). Moreover, one or both of the following clinical criteria had to be met for inclusion into the study: (a) an increase of serum creatinine by more than 15 % during the last 6 months and (b) the presence of proteinuria of at least 1 g/l for at least 2 months. Other reasons for an increase in serum creatinine, such as ureteral obstruction, cyclosporine nephrotoxicity, or changes in medication, had to be ruled out as much as possible. Patients with histological signs of a recurrence of the original kidney disease in the graft or with signs of acute rejection were excluded. Additional exclusion criteria were diabetes mellitus, pregnancy, prior malignancy, signs of cerebrovascular insufficiency, and angina pectoris or myocardial infarction during the preceding 6 months.

Study design

After they had given informed consent, patients were randomized to receive 200 µg misoprostol or matching placebo tablets four times daily, at meal times and before bedtime. The study was carried out in a double-blind fashion. Treatment was continued for 2 years or until the start of renal replacement therapy if this preceded the end of the treatment period. The reasons for premature withdrawal of a patient from the study were intractable side effects supposed to be caused by the study medication, changes in baseline immunosuppressive therapy (other than changes in dosage), start of an ACE inhibitor, and the occurrence of angina pectoris, myocardial infarction, or cerebrovascular insufficiency. The study protocol was approved by the ethics committees of the participating hospitals.

Analysis

Clinical and laboratory examinations were carried out as part of routine posttransplant patient care. Creatinine clearance was estimated according to the formula of Cockcroft and Gault. In patients with a duration of treatment exceeding 3 months, impairment of renal function was defined as a decrease in creatinine clearance of at least 5 % at the end of the follow-up, whereas an increase in proteinuria was defined as a rise in proteinuria of at least 0.5 g/day or 0.2 g/l. Based on the assumption that with misoprostol the frequency of impairment of renal function and/or increase of proteinuria would be reduced by 15 % or more, 100 patients should be enrolled to have an 80 % chance of detecting a difference between the study groups. However, patient enrolment appeared to lag expectations. Moreover, many patients had to be withdrawn from the study because of adverse effects. We, therefore, decided to end patient recruitment after inclusion of 40 patients and to analyze the data after a minimum duration of follow-up of the remaining patients of 1 year.

Results are given as medians with ranges. Between group comparisons of numerical data were carried out with Wilcoxon's rank-sum test. Proportions were compared by chi-squared analysis. Probabilities of survival were calculated by the Kaplan-Meier product-limit method and for comparison of survival curves the log-rank test was used. A P value less than 0.05 was considered statistically significant.

Results

Of the 40 study participants, 7 were included because of a rise in serum creatinine, 12 because of proteinuria, and 21 patients fulfilled both clinical inclusion criteria. There were no significant differences in clinical characteristics of the patients in the misoprostol and placebo group (Table 1). Median duration of treatment with study medication was 3.5 months (1–21) and 6.5 months (0–24) in the misoprostol and placebo group, respectively (NS). The tendency to a shorter duration of treatment in the misoprostol group was related to a higher frequency of withdrawal due to adverse effects (Table 2). In 6 of the 11 patients in whom misoprostol was discontinued because of adverse effects, treatment with a lower dosage had also appeared to be unsuccessful. The incidences of patient death, start of dialysis, impairment of renal function, and increase in proteinuria did not differ between the groups (Table 3). Estimated dial-

Table 2 Reasons for premature withdrawal from the study

	Misoprostol	Placebo	*P*
Intractable side effects	11 (50%)	3 (17%)	0.03
Change in base-line immunosuppression	1 (5%)	1 (6%)	NS
Start of an ACE inhibitor	0	2 (11%)	NS
Patient ends cooperation	2 (9%)	2 (11%)	NS

Table 3 Patient survival, graft function, and proteinuria

	Misoprostol ($n = 22$)	Placebo ($n = 18$)
Patient death	1 (5%)	3 (17%)
Graft failure	5 (23%)	6 (33%)
Impairment of renal function (including graft failure)[a]	11/16 (69%)	13/15 (87%)
Increase of proteinuria[a,b]	6/15 (40%)	6/12 (50%)

[a] In patients receiving study medication for at least 3 months
[b] Insufficient data in 4 patients

ysis-free survival at 1 year after the start of treatment was 60% in the misoprostol group and 84% in the placebo-treated patients (Fig. 1, NS). Sixteen misoprostol-treated patients and 7 patients receiving the placebo experienced one or more adverse effects ($P = 0.03$). The incidence of all side effects is given in Table 4.

Table 4 Adverse effects (The figure in brackets indicates the number of cases in which the particular side effect was the main reason for discontinuation of study medication)

	Misoprostol ($n = 22$)	Placebo ($n = 18$)
Diarrhea	10 (5)	4 (1)
Dyspepsia/nausea	10 (2)	5 (2)
Abdominal pain	4 (1)	2
Hypermenorrhoe	2 (2)	–
Infections necessitating hospitalization	1	2
Other	2 (1)	2

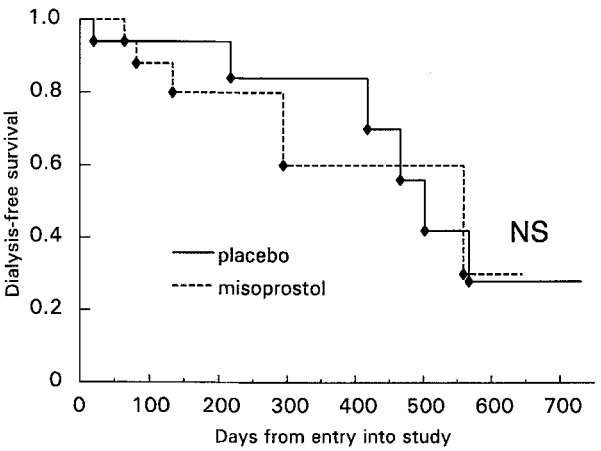

Fig. 1 Proportion of patients free of dialysis

Discussion

Our data do not indicate a favorable effect of misoprostol on the course of chronic rejection after renal transplantation. We recognize, however, that the small numbers of subjects and the short duration of follow-up do not allow for firm conclusions. This study was initiated after the promising results of Moran et al. [7] had been published. Since then, other trials have not confirmed the beneficial effect of misoprostol on acute rejection incidence and renal function after renal transplantation [2, 10, 14]. Taken together, there is no strong evidence for additive immunosuppressive efficacy of misoprostol in renal transplant recipients.

The high incidence of adverse effects, mostly of the gastrointestinal tract, was responsible for a substantial drop-out rate in the misoprostol group. Similar frequencies of side effects have been observed in other studies applying the same dosage of 800 μg/day [7, 14]. Although the side effects of misoprostol appear to be dose dependent [5], many of our patients who had to discontinue the drug did not tolerate a lower dosage either (data not shown). Based on the questionable immunosuppressive efficacy and the high rate of complications, we believe that further studies on the potential of misoprostol to influence the course of chronic rejection are not warranted.

Acknowledgements Searle Nederland B.V., Maarssen, The Netherlands, is gratefully acknowledged for providing the study medication.

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