Nephrol Dial Transplant (2004) 19: 3062–3067
doi:10.1093/ndt/gfh536
Advance Access publication 19 October 2004

Original Article

Nephrology
Dialysis
Transplantation

Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy

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Abstract

Background. Focal segmental glomerulosclerosis (FSGS) commonly presents with nephrotic syndrome (NS), and spontaneous remission is rare. NS is a poor prognostic marker for renal survival, and has serious extra-renal complications. Rapid remission using drugs with minimal side effects is desirable. Tacrolimus (Tac) has a more potent immunosuppressive effect and may be less toxic at therapeutic doses than ciclosporin (CsA). Although CsA has a role in the treatment of FSGS, there are limited data regarding the use of Tac monotherapy in this setting, and this is limited to experience in children.

Methods. We prospectively report the outcome for six adult patients with FSGS treated with Tac from first presentation with NS, and for a further five adult patients in remission on CsA converted to Tac in an attempt to arrest a progressive decline in renal function on CsA.

Results. All six patients treated with Tac from presentation with NS achieved remission after 6.5 ± 5.9 months. The serum albumin for the group increased from 26.8 ± 4.6 to 37.7 ± 1.9 g/l ($P = 0.003$), and there was a significant reduction in the mean 24 h urinary protein excretion from 11.0 ± 4.5 to 2.8 ± 2.5 g ($P = 0.003$). All remissions were partial with a mean reduction in 24 h urinary protein of $75.2 \pm 16.8\%$. There was a non-significant reduction in MDRD GFR from 71.7 ± 22.4 to 55.9 ± 9.7 ml/min/1.73 m^2 ($P = 0.07$), which manifest within the first 3 months of Tac treatment but renal function was subsequently stable. The mean follow-up for the group was 12.8 ± 5.5 months. Two of the five patients converted from CsA to Tac maintained complete remission, and the remaining three patients in partial remission had further reductions in proteinuria. There was an improvement in renal function concomitant with conversion to Tac in each case, with an overall improvement in MDRD GFR for the group of $+1.9 \pm 1.1$ ml/min/1.73 m^2/month.

Conclusions. Tac rapidly and effectively induced remission of NS in FSGS. Conversion from CsA to Tac indicates that Tac might be a more potent agent with less nephrotoxicity in this setting.

Keywords: focal segmental glomerulosclerosis; nephrotic syndrome; tacrolimus

Introduction

The extensive review by Korbet *et al.* [1] of the clinical course of FSGS places the importance of treatment of nephrotic syndrome (NS) in this condition in context. The majority of adults with focal segmental glomerulosclerosis (FSGS) present with NS, and spontaneous remission is rare [1]. Failure to remit from NS is associated with poor renal survival, with 50% reaching end-stage renal failure after 6–8 years [1]. The amount of proteinuria also correlates with renal survival [1]. Complete remission is therefore highly desirable to preserve renal function.

NS is a major risk factor for cardiovascular disease, with a relative risk of death from coronary artery disease of 2.8 [2]. It is also associated with a hypercoaguable state that predisposes to both venous and arterial thromboses [3], and an increased risk of infection as a result of hypogammaglobulinaemia and renal insufficiency [4]. The use of ACE inhibitors (ACE-I) and angiotensin receptor antagonists (ARA) to control blood pressure and proteinuria, and thereby reduce the risk of adverse renal and cardiovascular events is well documented [5]. In addition HMG CoA reductase inhibitors (statins) have been shown to ameliorate the hyperlipidaemia and endothelial dysfunction associated with NS [6].

It has long been postulated that for a subset of patients with nephrotic FSGS, a T-cell driven injury

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might be responsible for the loss of the selective permeability of the glomerular barrier and podocyte injury that is seen, and immunosuppressive agents have an established role in their treatment. Corticosteroids induce remission in >30% of patients in most studies [1], and later studies have illustrated the importance of longer treatment courses but also their incumbent side effects [7]. Cytotoxic agents sustain remission when there is steroid-dependency, but are less efficacious when there is steroid-resistance, and also have serious side effects [1]. Calcineurin inhibitors may be a useful alternative with less toxicity. Ciclosporin (CsA) has been shown to be effective in randomized controlled studies of steroid-dependent and steroid-resistant idiopathic NS [8,9]. More specifically, in randomized controlled trials of steroid-resistant FSGS in adults, the group receiving CsA and low-dose prednisolone had better renal function and remission rates than the group who received a placebo and prednisolone [10]. However, a high relapse rate was noted on cessation of treatment [10], and prolonged treatment may be associated with chronic nephrotoxicity [11].

This study tests the hypothesis that tacrolimus (Tac) monotherapy is effective at inducing remission of NS in FSGS. Tac has been shown to be a more potent immunosuppressant than CsA in the setting of cadaveric renal transplantation [12]. There is also some evidence that the acute adverse effects that may be contributory to the chronic interstitial scarring associated with calcineurin inhibitors may not be as marked for Tac [13]. There have been encouraging results from a prospective uncontrolled study of the treatment of NS with Tac in combination with corticosteroids in 25 adults with CsA-resistant and CsA-dependent FSGS [14]. To date, there is only one pilot study of Tac monotherapy in four children with FSGS [15].

This is a prospective observational study of the use of Tac monotherapy to treat adults with FSGS from first presentation with NS at a single UK centre. We also describe the effects of conversion from CsA to Tac for adults with FSGS in established remission from NS but with declining renal function.

Patients and methods

Treatment of patients presenting with NS

All six patients with biopsy-proven FSGS and NS treated with Tac at our centre were included in this study (Table 1). Secondary conditions associated with FSGS were excluded, patients were not analysed for podocin mutations, but subsequent response to Tac makes these unlikely. The mean age of this patient group was 45.9 ± 7.7 years. There were three males and three females. Two patients were Caucasian, three were South Asian and one was Afro-Caribbean. NS was defined by the presence of oedema, with a serum albumin of <35 g/l and a 24 h urinary protein excretion of >3.5 g. The mean serum albumin was 26.8 ± 4.6 g/l, with a mean 24 h urinary protein excretion of 11.0 ± 4.5 g (Table 2). One patient had suffered from a pulmonary embolus. The glomerular filtration rate was estimated using the abbreviated Modification of Diet in Renal Disease formula (MDRD GFR), which does not include serum albumin as a variable [16]. The mean MDRD GFR for the group at the start of Tac treatment was 71.7 ± 22.4 ml/min/1.73 m^2 (Table 2).

Consent for treatment with Tac was obtained from patients after a full explanation of the treatment options and potential side effects. The mean duration of NS for the group prior to Tac treatment was 13.6 ± 11.8 months, and during this period non-immunosuppressive treatment with ACE-I and ARA was optimized to reduce systemic blood pressure to a target of ≤120/80 mmHg. Mean systolic and diastolic blood pressures were calculated from the three measurements made prior to the start of Tac treatment, and the three most recent measurements. The serum total cholesterol at the start of Tac treatment and at follow-up was measured. Statins were used to reduce total cholesterol to a target of <5 mmol/l. Those patients with a serum albumin of ≤25 g/l were initially treated with enoxaparin 20 mg subcutaneously once daily and were converted to aspirin 75 mg orally once daily when their serum albumin had risen above this level. The patient with a pulmonary embolus was converted to daily warfarin treatment with a target international normalized ratio of 2.

None of the patients had previously been treated with a calcineurin inhibitor, an alkylating agent or corticosteroids. Hepatitis B and C, and HIV were excluded by serological tests in all patients before treatment with Tac.

Tac was started at 2 mg orally twice daily and the dose was subsequently adjusted according to levels. Twelve hour trough Tac levels were measured at each clinic visit by MEIA Tacro II assay (Abbott Diagnostics, UK), until July 2003 when an assay based on tandem mass spectrometry was introduced. The Tac dosage was altered to achieve 12 h trough levels within the range 4–7 ng/ml. No one was started on corticosteroids with the initiation of Tac treatment.

Remission was defined as the time at which serum albumin first normalized (≥35 g/l by local standard) with clinical resolution of oedema. The remission was defined as partial if serum albumin had normalized and 24 h total protein excretion had reduced by at least a 50% but had remained >0.4 g.

Table 1. Demographics of patients with NS

Number (male:female)	6 (3:3)
Age (years)	45.9 (± 7.7)
Ethnicity	2 Caucasian, 3 South Asian, 1 Afro-Carribean
Duration of NS (months)	13.6 (± 11.8)

Table 2. Results of treatment with Tac for NS

	At presentation	At follow-up	*t*-Test
Serum albumin (g/l)	26.8 (± 4.6)	37.7 (± 1.9)	$P = 0.003$
Urinary protein excretion (g/24 h)	11.0 (± 4.5)	2.8 (± 2.5)	$P = 0.003$
MDRD GFR (ml/min/1.73 m^2)	71.7 (± 22.4)	55.9 (± 9.7)	$P = 0.07$

Conversion to from CsA to Tac for patients in established remission from NS with declining renal function

Five patients with FSGS in established remission but with declining renal function were converted from CsA to Tac (Table 3). The mean age of the group was 40.7 ± 15.2 years. Two were male and three were female. Four were Caucasian and one was Afro-Caribbean. The mean duration of FSGS was 8.1 ± 9.0 years. There were no previous thromboembolic complications. All five patients had been treated with CsA and corticosteroids. All were CsA-dependent and had been in remission on treatment for a mean of 17.2 ± 5.9 months with a mean serum albumin of 41.6 ± 4.8 g. The mean maintenance CsA dose was 3.9 ± 1.0 mg/kg/day in two divided doses prior to conversion to Tac, with a mean 12 h trough CsA level of 155 ± 62 ng/ml. Corticosteroids had been stopped successfully in three out of the five patients, with the remaining two patients on a maintenance dose of prednisolone 5 mg orally daily when Tac was started. Two patients were in complete remission with 24 h urinary protein excretion of <0.4 g, and three patients were in partial remission, the 24 h urinary protein excretion for the group as a whole was 1.5 ± 1.3 g. The mean MDRD GFR for the group was 43.6 ± 13.9 ml/min/1.73 m^2 (Table 4). The mean rate of decline in GFR on CsA was −1.6 ± 0.7 ml/min/1.73 m^2/month (Figure 4).

Patients were consented and converted to Tac treatment at an initial dose of 2 mg orally twice daily. The dose of Tac was subsequently altered according to 12 h trough levels seeking the target range 4–7 ng/ml.

Statistics

The mean ± 1 standard deviation are reported. Parametric data was compared using a paired two-tailed Student's *t*-test (Microsoft Excel 2002), with significance taken as $P < 0.05$.

Results

Treatment of patients presenting with NS

The group was followed up for a mean of 12.8 ± 5.5 months. The mean Tac dose was 0.07 ± 0.03 mg/kg/day; a mean trough level of 5.5 ± 1.2 ng/ml was achieved. All six patients went into remission, achieving an increase in serum albumin into the normal range, with resolution of their oedema. There was a rise in mean serum albumin from 26.8 ± 4.6 to 37.7 ± 1.9 g/l ($P = 0.003$) and the mean time to remission was 6.5 ± 5.9 months (Table 2 and Figure 1). There was a significant reduction in mean 24 h urinary protein excretion for the group as a whole from 11.0 ± 4.5 to 2.8 ± 2.5 g ($P = 0.003$) (Table 2 and Figure 2). All were partial remissions with a mean reduction in 24 h urinary protein excretion of 75.2 ± 16.8%. There were no relapses, with all patients remaining on Tac at the end of the study.

There was a decrease in mean MDRD GFR at follow-up from 71.7 ± 22.4 to 55.9 ± 9.7 ml/min/1.73 m^2 although not statistically significant ($P = 0.07$) (Table 2). Two patients showed a decline in MDRD GFR within the first 6 months of treatment (open and closed squares, Figure 3), but subsequent to this it apparently stabilized. For the remaining four patients (Figure 3), renal function appeared more stable from the outset.

There was no significant change in either mean systolic or diastolic blood pressure following Tac treatment (from 150 ± 26 to 131 ± 13 mmHg, $P = 0.08$, and from 88 ± 9 to 80 ± 6 mmHg, $P = 0.1$, respectively). There was a significant reduction in the mean serum total cholesterol (from 9.1 ± 3.3 to 5.1 ± 1.7 mmol/l, $P = 0.05$).

Conversion from CsA to Tac for CsA-dependent patients with declining renal function

The mean follow-up for the group was 16.1 ± 6.2 months. The mean Tac dose for the group was 0.1 ± 0.04 mg/kg/day, with a mean 12 h trough level of 6.4 ± 2.4 ng/ml. All five patients were in remission at follow-up, the mean serum albumin at follow-up for

Table 3. Demographics of patients converted from CsA to FK

Number (male:female)	5 (2:3)
Age (years)	40.7 (± 15.2)
Ethnicity	4 Caucasian, 1 Afro-Carribean
Duration of FSGS (years)	8.1 (± 9.0)
Duration of remission on CsA (months)	17.2 (± 5.9)

Table 4. Results of conversion from CsA to FK

	At conversion	At follow-up	*t*-Test
Serum albumin (g/l)	41.6 (± 4.8)	39.6 (± 4.0)	$P = 0.39$
Urinary protein excretion (g/24 h)	1.5 (± 1.3)	0.8 (± 0.7)	$P = 0.08$
MDRD GFR (ml/min/1.73 m^2)	43.6 (± 13.9)	49.7 (± 21.8)	$P = 0.2$

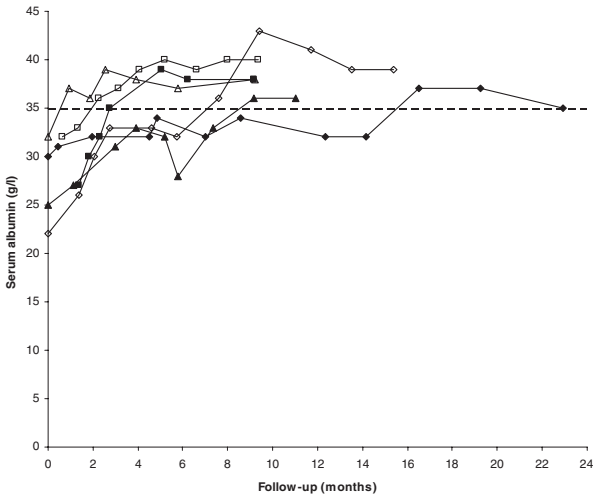

Fig. 1. Change in serum album with Tac treatment of patients with NS and FSGS.

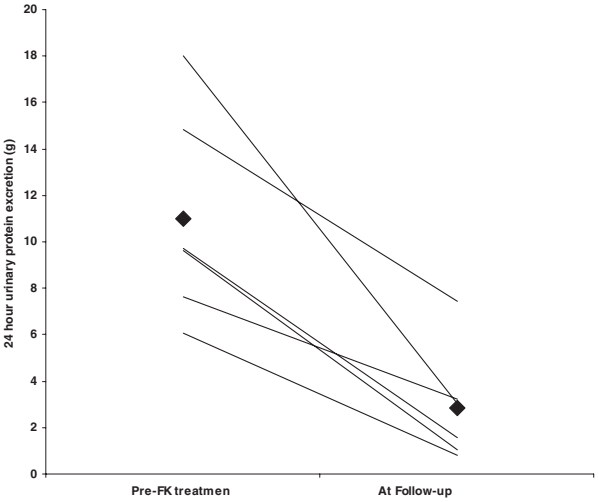

Fig. 2. Change in 24-hour urinary protein excretion with Tac treatment of patients with NS and FSGS (diamonds, mean values).

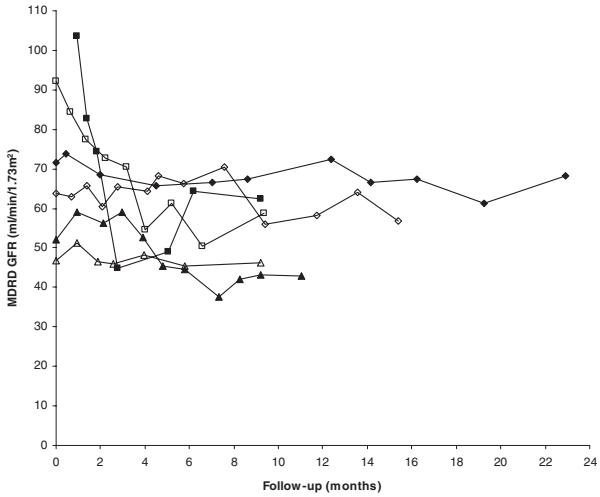

Fig. 3. Change in renal function with Tac treatment of patients with NS and FSGS.

the group was not statistically different from that at the time of conversion, 41.6 ± 4.8 *vs* 39.6 ± 4.0 g/l ($P = 0.39$) (Table 4). Remission remained complete for the two patients in complete remission at the time of conversion, with a further reduction in 24 h urinary protein excretion for those in partial remission at the time of conversion. The mean 24 h urinary protein excretion for the group as a whole fell from 1.5 ± 1.3 to 0.8 ± 0.7 g, although this did not reach significance ($P = 0.2$) (Table 4). The mean MDRD GFR for the group increased from 43.6 ± 13.9 to 49.7 ± 21.8 ml/min/1.73 m^2 but this did not reach significance ($P = 0.2$) (Table 4). The mean MDRD GFR was declining at a rate of -1.6 ± 0.7 ml/min/1.73 m^2/month from the time CsA was started to the time of conversion from CsA, but was improving at a rate of $+0.3 \pm 0.5$ ml/min/1.73 m^2/month from the time Tac was started to the time of follow-up on Tac, representing a net gain in mean MDRD GFR of $+1.9 \pm 1.1$ ml/min/1.73 m^2/month ($P = 0.02$) (Figure 4).

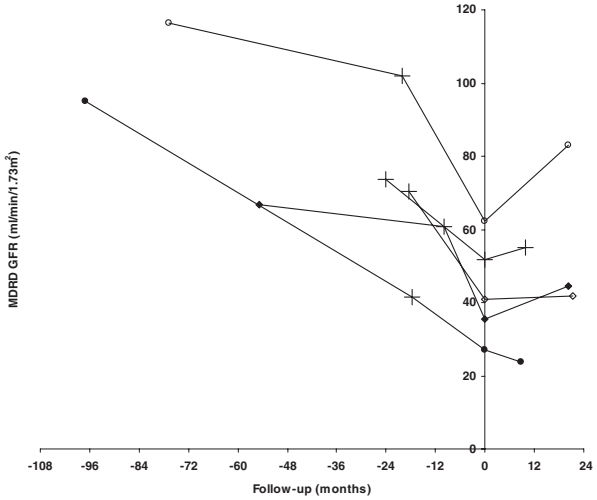

Fig. 4. Change in renal function in FSGS patients converted from CsA and corticosteroids to Tac treatment. All patients treated with CsA and corticosteroids were in established remission but had declining renal function (+, start of CsA and corticosteroids; time zero, conversion to Tac).

Two out of five patients relapsed during the course of follow-up. One patient relapsed at 2.2 months post-conversion, 12 h trough levels up to that point had been at the low end of the target range, but at the time of relapse the 12 h trough level of 3.5 ng/ml was sub-therapeutic. The Tac dose was increased and the patient achieved remission again after 6.4 months. The other patient relapsed after 7.3 months of Tac treatment, he admitted to non-compliance with his treatment although presumably this was variable as his mean Tac level was 7.9 ± 1.9 ng/ml. He achieved remission again after 2.1 months. Tac was successfully withdrawn at 12 months for one patient in sustained complete remission, and there was no relapse in the subsequent 4.1 months follow-up.

At the start of Tac treatment the mean total cholesterol was 4.6 ± 1.2 mmol/l and the mean blood pressure was 130 ± 9 mmHg systolic and 78 ± 4 mmHg diastolic. The mean systolic and diastolic blood pressures at follow-up were not statistically different at 130 ± 10 ($P = 0.9$) and 80 ± 5 mmHg ($P = 0.7$), respectively. The mean total cholesterol at follow-up was not statistically different at 4.4 ± 1.0 mmol/l ($P = 0.7$).

Adverse effects of Tac

Tac was well tolerated with no side effects. After 131 patient months follow-up, there was one urinary tract infection, but this patient did not require hospitalization. One patient suffered from an acute episode of nephrotoxicity, treated by brief cessation of Tac and then reinstitution at a lower dose. He was 47 years old and had been converted from CsA to Tac. He had an accidental overdose after 4.3 months of treatment with Tac. His highest 12 h trough Tac level was 14.8 ng/ml and his mean Tac level for the period of study was 4.5 ± 3.3 ng/ml. Renal function at the start

of treatment for this patient was 51.9 ml/min/1.73 m^2 and at follow-up was 54.9 ml/min/1.73 m^2.

Discussion

The results of this prospective study show that the use of Tac alone is effective for the treatment of NS with remission in 6/6 patients with FSGS, with a mean reduction in proteinuria of 75.2 ± 16.8% for the group as a whole.

This study confirms the results of a pilot study of Tac monotherapy in four children with FSGS [15]. Three children who had received prednisolone and CsA either alone or in combination with cyclophosphamide had responded only partially, the fourth child had not responded to prednisolone and cyclophosphamide. Tac induced complete remission for one child and partial remission for the other three. There was one prospective uncontrolled study of the use of Tac in combination with corticosteroids in 25 patients with CsA-resistant and CsA-dependent FSGS. 48% of patients remitted, and a further 20% had reduced proteinuria [14].

Withdrawal of CsA after a 6-month course of treatment was associated with relapse rates of 60% in patients with FSGS after 18 months follow-up [10], and a relapse rate of 76% was seen in the study of Tac in combination with corticosteroids for FSGS [14]. In our study, none of the six patients treated for NS have relapsed but all remained on treatment at the end of the study. Two of the five patients in the conversion group relapsed although this was likely to be related to low levels for one patient and intermittent compliance for the second. The optimal length of treatment has yet to be defined. Tac treatment was successfully withdrawn for one patient in the conversion group after 12 months sustained complete remission. It is hoped that longer durations of treatment will result in a reduced rate of relapse but further studies are required to confirm this.

There was a non-significant decline in MDRD GFR mainly contributed to by an initial decline within 6 months of treatment for two patients that then apparently stabilized. Renal function for the other four patients appeared stable throughout follow-up. The number of cases was small and the follow-up was short precluding definite conclusions about the long-term tolerability of Tac. Calcineurin inhibitor toxicity is a concern but so is progressive disease. In a study of the long-term tolerance of CsA for patients with FSGS, the number of FSGS lesions on biopsy increased in some patients irrespective of whether CsA had induced remission, and interstitial fibrosis was most marked in those with progressive glomerulopathy and few were characteristic of calcineurin-inhibitor toxicity [17].

Systolic and diastolic blood pressures were not significantly different at follow-up, and it is reassuring that Tac does not result in problems with resistant hypertension. The mean total cholesterol was significantly reduced during treatment with Tac. Remission from NS and increasing doses of statins are likely to account for this reduction. Tac has been generally well tolerated in this study although follow-up so far is short. Tac has been used at higher levels and for a longer duration in the renal transplant population with a reasonable side effect profile but this will need to be carefully monitored in this group of patients.

The conversion to Tac from CsA for a further five patients in remission with declining renal function with CsA-dependent FSGS was associated with an improvement in renal function and a further reduction in proteinuria, although neither reached statistical significance. A direct comparison of Tac and CsA in the transplant setting has suggested that Tac may be less nephrotoxic at therapeutic levels. Renal function improved significantly when liver transplant recipients were converted to Tac from CsA for nephrotoxicity [18], and long-term experience following randomization of renal transplant recipients to either Tac or CsA at a single centre has shown superior renal function, less progressive interstitial fibrosis and better graft survival in the group treated with Tac [19].

In conclusion, Tac appears to be an effective treatment for FSGS at least in the short-term. It is speculated that the reduction in proteinuria and immunomodulation of the disease process will lead to increased renal survival in these patients. However, the effects of Tac on renal function in larger long-term trials are needed to assess its safety and efficacy in terms of disease progression and renal failure with resort to renal biopsy where necessary.

Acknowledgements. We would like to thank the staff of our nephrology clinics whose care and attention to detail has been a major contribution to this work. Presented in part as a poster at the American Society of Nephrology Renal Week 2003, *J Am Soc Nephrol* 2003; 14: 524A (abstract SA-PO1026).

Conflict of interest statement. The authors state that neither this manuscript nor any significant part of it is under consideration for publication elsewhere, or has appeared elsewhere in a manner that could be construed as a prior or duplicate publication of the same, or very similar, work. The authors do not have any significant primary financial arrangements with commercial companies that produce or sell Tac that is the subject of this manuscript.

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Received for publication: 7.6.04
Accepted in revised form: 7.9.04