ORIGINAL ARTICLE

Angiotensin II type 1 receptor antagonists reduce proteinuria of hypertensive renal transplant recipients

Vergoulas G, Miserlis Gr, Papanikolaou V, Karasavvidou F[1], Leontsini M[1], Gakis D, Pantzaki A[1], Atmatzidis E, Takoudas D, Antoniadis A

Organ Transplant Unit, Aristotle University of Thessaloniki, Hippokration General Hospital of Thessaloniki, Greece
[1] Histopathology Department, Hippokration General Hospital of Thessaloniki, Greece

The aim of this study was to investigate the safety and efficacy of angiotensin II receptor type 1 antagonists (AT1RA) on hypertensive renal transplant recipients with proteinuria. Eighteen pts with hypertension and proteinuria were included in the study. These pts (14 male, 4 female) with a mean age 48 years (range 31 to 64 years) received AT1RA (11 losartan, 7 valsartan) 4.33 years after Rt (0.5 to 11 years). All of them had a six month follow up before and after the initiation of AT1RA. Systolic (SBP) and diastolic blood pressure (DBP), serum creatinine (Scr) and Hb were recorded every two months during the follow up period. Proteinuria (Pr), number of antihypertensive agents (NAA) and cyclosporine levels (CyAl) were recorded at AT1RA treatment initiation and six months later. ANOVA for repeated measures and paired sample t test were used for statistical analysis.

SBP/DBP measurements were 143.12±14.00/ 90.31±10.07 mmHg, 146.87±10.62/ 90.00±7.30 mmHg, 148.12±12.63/93.75±8.85 mm Hg, and 146.25±13.96/ 86.25±5.91 mmHg 6,4,2 and 0 months before AT1RA initiation respectively (p:NS) and 139.33±14.8/85.33±5.49 mmHg, 143.66±17.05 /86.00±8.06 mmHg and 142.33±10.99/87.33±8.42 mmHg 2,4 and 6 months after AT1RA initiation respectively (p:NS). Scr was 1.53±0.55 mg/dl, 1.61±0.70 mg/dl, 1.66±0.70 mg/dl and 1.68±0.71 mg/dl 6, 4, 2 and 0 months before AT1RA initiation respectively (p:NS) and 1.78±0.80 mg/dl, 1.84±0.87 mg/dl and 1.82± 0.94 mg/dl 2, 4 and six months after AT1RA initiation respectively (p:NS). Hb was 12.80±2.11 g/dl, 12.57±1.78 g/dl, 12.73 ± 1.80 g/dl and 12.26±2.09 g/dl 6,4,2 and 0 months before AT1RA initiation respectively and 12.10±1.69 g/dl, 11.48±1.59 g/dl and 11.55±1.62 g/dl 2, 4 and 6 months after AT1RA initiation respectively (p:0.005). Pr was 0.76±0.77 g/dl g/24 h before and 0.61±0.63 g/24 h six months after AT1RA initiation (p:0.024). The NAA was 2.27±0.89 and 1.83±0.85 before and six months after AT1RA initiation (p:0.007). CyAl were 83.75±42.22 and 70.24±40.16 ng/L before and after AT1RA treatment (p:NS).

In conclusion AT1RA reduce statistically significantly renal transplant recipient's proteinuria, control their hypertension efficiently, reduce the number of antihypertensive agents needed, do not cause impairment of renal function and cause a small but statistically significant fall of Hb.
Hippokratia 2001, 5 (4): 165-171

The aetiology of proteinuria in patients with a renal allograft is diverse including acute allograft rejection, de novo glomerulonephritis (GN), recurrent GN, cyclosporine toxicity, chronic allograft nephropathy and small nephron number[1]. Despite the fact that proteinuria and progression of renal disease have not been linked with a definite pathophysiological mechanism, it is generally accepted that proteinuria is a bad prognostic marker in the progression of renal disease and that proteinuria per se plays a role in the progression of renal disease.

Oral presentation at the 5th BANTAO Congress, September 30 - October 3, 2001, Thessaloniki, Greece

All studies conducted on renal transplant recipients conclude that proteinuria is an excellent marker of poor graft prognosis[2]. Massy and co workers showed that the prevalence of proteinuria exceeding 0.5 g/day is four times higher in patients with chronic allograft failure than in patients with stable graft function[3]. Also the composition of urinary proteins seems to be of great importance since selective albuminuria has a much better prognosis than non-selective proteinuria[4,5].

Several mechanisms have been proposed by which proteinuria per se might cause renal damage and the most prevalent is the interstitial damage[6]. The prolonged over-reabsorption of protein by the renal tubules results in the activation of pro-inflammatory pathways, which trigger inflammation in the interstitium. It is the severity of the resultant interstitial fibrosis that correlates most closely with the degree of renal impairment and subsequent prognosis. It has been proposed that increased reabsorption of proteins by tubular epithelial cells, leads to lysosomal swelling and rupture, resulting in contamination of the cytoplasm with injurious lysosomal enzymes. Some proteins such as transferrin might be especially toxic. Transferrin delivers iron to the intracellular acidic environment, where these ions catalyse the formation of reactive oxygen species, causing peroxidative cell injury. Oxidative modification might also alter filtered and reabsorbed proteins, which are specifically bound by membrane receptors and recycled within the cytoplasm. Overloading of proximal tubular cells in culture with albumin or transferrin-iron upregulates the gene of monocyte chemoattractant protein (MCP-1). Also complement components filtered during proteinuria can be activated on the brush border of the proximal tubular cells with a consequent insertion of membrane attack complex onto the tubular cell membrane. Cytoskeletal alterations and cytolysis follow as well as generation of TNF-a and IL-6[7,8].

Other possible mechanisms of proteinuria associated recruitment of mononuclear cells in the interstitial compartment are 1) expression of HLA class II molecules by the renal tubular epithelial cells and their recognition by the recipient's T-cells. Glomerular basement membrane material shed into the urine may be reabsorbed by the tubules and presented to the T cells[9-12]. Additionally intracellular adhesion molecule-1 (ICAM-1) and HLA class II molecule expression has been especially noted during acute rejection episodes. The importance of ICAM-1 in the induction of interstitial nephritis has been shown recently[13], 2) proteinuria causes a dose dependent elevation in synthesis and release of endothelin-1 (ET-1) in the proximal tubular cells. This upregulation may cause increased tone of afferent and efferent arteriols, reducing the blood supply to peritubular capillaries. ET-1 accumulation in the renal interstitium could promote interstitial fibroblast proliferation, matrix deposition and infiltration of active macrophages[7,14,15].

Studies performed using angiotensin converting enzyme inhibitors have demonstrated a beneficial effect of modulating the renin angiotensin system in proteinuric conditions and renal diseases[16]. These effects are secondary to a reduction to angiotensin II formation and are in part independent of the drug's ability to lower systemic blood pressure. Angiotensin II plays a central role in the pathogenesis of progressive renal disease through the stimulation of cell growth, extracellular matrix deposition, and the synthesis of chemoattractants[17].

The therapeutic interventions to reduce proteinuria include, until now, dietary protein restriction[18], ACE inhibitors[19] and calcium channel blockers[20]. We already have shown that AT1RA are effective agents in the control of blood pressure of hypertensive renal transplant recipients[21,22]. In this study we investigated the efficacy of AT1RA in reducing the proteinuria of hypertensive renal transplant recipients.

Patients and methods

Eighteen renal transplant recipients (14 men, 4 women) on antihypertensive therapy were selected to receive losartan (11) or valsartan (7) in an outpatient basis at Hippokratio General Hospital of Thessaloniki. The previous antihypertensive treatment was interrupted and they were given losartan or valsartan because of proteinuria more than 0.25 g/24 h. Blood pressure measurement was done in the morning between 9.00 and 11.00 am. Patients were excluded from the study if they had heart failure, major arrhythmias, myocardial infarction or stroke within the previous six months.

Their mean age was 47.62±11.30 years (range 30.54-63.78 years). They had received triple or quadruple sequential drug immunosuppression. No patient had documented renal artery stenosis. Patients' demographic data are shown in table 1. No patient had salt depletion or any active disease at the time of drug initiation. The initial dose of losartan and valsartan was given according to the needs of each patient. In cases with inadequate control there was a rapid augmentation of the dose at weekly intervals up to the dose of 100 mg/d and 160 mg/d respectively, according to recommendations of the product companies. If it was necessary other antihypertensive drugs were added in patients regimen.

Table 1. Demographic data

-Male/female	**14/4**
-Mean age (years)	47.62±11.30
range	30.54 - 63.78
-Primary renal disease	
Glomerulonephritis	7
Interstitial nephritis	3
Hypertensive glomerulopathy	1
Polycystic kidney disease	1
Diabetic nephropathy	1
Unknown aetiology	5
-Reason for inclusion in the study	
Proteinuria	> 250 mg/24 h
-Mean time from Rt (years)	4.33±2.56
range	0.51 – 10.64

Blood pressure measurement was done with the patient at sitting position, always by the same automated machine (auscilometric). Blood and urine samples were taken, after overnight fasting on outpatient basis, at starting time and 2, 4 and 6 months after losartan or valsartan initiation. Serum creatinine and Hd, were measured at the same time intervals. Proteinuria (24 hour urine protein), drug dose, number of antihypertensive agents and cyclosporine levels were measured before the day of AT1RA initiation and six months later.

Repeated measures analysis was used to estimate the effect of the drugs on measured parameters during time. Paired samples' t test was used appropriately to compare quantitative variables at time 0 and 6 months after treatment initiation with AT1RA. A value of $p < 0.05$ was considered statistically significant (ss). Quantitative results were expressed as Mean ± SD. The statistical package SPSS for windows, version 10.1, was used.

Results

Proteinuria was measured at time zero and six months after AT1RA initiation and showed a statistically significant fall (table 2). The antihypertensive drugs needed, measured at the same time intervals, also showed ss fall (table 2). The mean levels of systolic and diastolic blood pressure measured at bimonthly intervals six months before and six months after the initiation of AT1RA did not show significant change during time (table 3, 4). Mean serum creatinine levels measured at bimonthly intervals six months before and six months after AT1RA initiation did not show significant change during time (table 5). The patients with proteinuria reduction did not show any beneficial effect on their renal excretory function. Mean haemoglobin levels measured at bimonthly intervals were stable before AT1RA initiation while they fell ss during the six month period follow up after AT1RA initiation (table 6).

The CyA levels measured at the beginning of treatment with AT1RA and at the end of the six month follow up did not show ss difference (table 7). Two of our patients presenting proteinuria with normal serum creatinine refused allograft biopsy and in one case there was inadequate tissue sampling. Seven patients had a history of acute rejection documented with renal biopsy. Seven patients without history of acute rejection proved to have CAN, and another de novo GN (table 8). We could not find any relation between histology and behaviour of proteinuria after AT1RA treatment.

Discussion

Until now AT1RA therapy is used with caution in renal transplant recipients. Although most recent studies show reduction of blood pressure, there are no data as to whether this treatment has a beneficial or not effect on the declining excretory function in cases of chronic renal transplant disease on the long term.

Proteinuria, except of being a marker of renal damage, is also a factor that can cause or contribute to renal damage through a toxic effect on the proximal tubular epithelial cell acting like

Table 2. Proteinuria and number of antihypertensive drugs the day before initiation of treatment with AT1RA and six months later

	BLM* before AT1ARA initiation	Six months later
24 hour urine protein (g)	0.76 ±0.77[1]	0.61±0.63[1]
range	0.25-2.50	0.00-1.80
Number of antihypertensive agents	2.27±0.89[2]	1.83±0.85[2]

[1] p: 0.024 [2] p:0.007 *baseline measurement

Table 3. Levels of systolic blood pressure measured at bimonthly intervals the six month period before AT1RA initiation and six month period after (mm Hg)

months	-6	-4	-2	BLM*
before AT1ARA (mm Hg)	143.12±15.78	146.87±10.62	148.12±12.63	146.25±13.96
months	**BLM***	**+2**	**+4**	**+6**
after AT1ARA (mm Hg)	146.25±13.96	139.33±11.62	143.66±17.05	142.33±10.99

p:NS, *baseline measurement before changing the drugs

Table 4. Levels of diastolic blood pressure measured at bimonthly intervals the six month period before AT1RA initiation and six month period after (mmHg)

months	-6	-4	-2	BLM*
before AT1ARA (mm Hg)	90.31±10.07	90.00±7.30	93.75±8.85	86.33±6.39
months	**BLM***	**+2**	**+4**	**+6**
after AT1ARA (mm Hg)	86.33±6.39	85.33±5.49	86.00±8.06	87.33±8.42

p:NS, *baseline measurement before changing the drugs

Table 5. Mean serum creatinine levels measured at bimonthly intervals before and after AT1RA initiation

months	-6	-4	-2	BLM*
serum creatinine before (mg/dl)	1.53±0.55	1.61±0.70	1.66±0.70	1.70±0.78
months	**BLM***	**+2**	**+4**	**+6**
serum creatinine after (mg/dl)	1.70±0.78	1.78±0.80	1.84±0.87	1.82±0.94

p:NS, *baseline measurement before changing the drugs

Table 6. Mean Hb levels measured at bimonthly intervals before and after AT1RA initiation

months	-6	-4	-2	BLM*
Hb before (g/dl)	12.80±2.11	12.57±1.78	12.73±1.80	12.32±2.17
months	**BLM***	**+2**	**+4**	**+6**
Hb after (g/dl)	12.32±2.17[1]	12.10±1.69[1]	11.48±1.59[1]	11.55±1.62[1]

[1]p:0.005, *baseline measurement before changing the drugs

Table 7. Cyclosporine levels and AT1 at starting day and six months after AT1RA initiation

	BLM* before AT1ARA initiation	Six months later
Cyclosporine levels (ng/ml)	83.73±42.22	70.24±40.16

p:NS, *baseline measurement before AT1RA initiation

Table 8. Histologic findings on allograft biopsies and response of proteinuria to AT1RA

	Histology	response to AT1RA
Patient No 1	Refused biopsy	no
Patient No 2	Acute rejection	yes
Patient No 3	Acute rejection	yes
Patient No 4	Acute rejection	no
Patient No 5	Acute rejection + CAN[1] + CsA toxicity	yes
Patient No 6	CAN	yes
Patient No 7	Acute rejection + CAN	yes
Patient No 8	Inadequate renal tissue	yes
Patient No 9	Acute rejection + CAN + CsA toxicity	no
Patient No 10	CAN + borderline rejection	yes
Patient No 11	CAN grade II	no
Patient No 12	CAN + CAG[2]	yes
Patient No 13	CAN	yes
Patient No 14	Refused biopsy	yes
Patient No 15	CAN + CsA toxicity	yes
Patient No 16	Late acute rejection + CAN	no
Patient No 17	CAN	no
Patient No 18	De novo GN[3]	no

[1]CAN: Chronic allograft nephropathy
[2]CAG: Chronic Allograft glomerulopathy
[3]GN: Glomerulonephritis

a signalling molecule[6,23,24]. It has been proposed that the presence of excessive protein in tubular fluid of proteinuric renal disease enhances the proinflammatory effects of angiotensin II and contributes to the development of interstitial fibrosis. In a retrospective study of renal graft recipients with declining graft function there was stabilization of renal function of patients who had a reduction of their fractional protein excretion during treatment with ACE inhibitors[25].

Our retrospective study, based on the observations that AT1RA have similar effect, on blood pressure and proteinuria on experimental models and patients with chronic renal disease, with that of ACE inhibitors[26,27], showed ss reduction of 24 hour proteinuria after six month treatment of hypertensive renal transplant recipients with AT1RA. Our results are in agreement with the three month duration study of Del Castillo et al[28]. Proteinuria became zero in 3 of our patients, reduced in 8, remained stable in 4 and increased slightly in 3 patients.

During the one year follow up there was a tendency for serum creatinine to increase but this change was not significant neither before, nor during the six month AT1RA treatment. We were not able to find any improvement in renal function (serum creatinine) of the 11 patients with reduction of proteinuria during time. One might criticize that serum creatinine is not a sensitive marker and the decline of renal function is not linear in patients with chronic allograft disease[29] and therefore the use of a patient as his own control might not be acceptable. But we already know that over time progression of chronic transplant failure tends to accelerate in renal allograft recipients[30] and the use of these drugs on hypertensive renal transplant recipients with normal graft function without proteinuria is usually accompanied with a slight but ss increase in serum creatinine level[21,22,28]. From this point of view we should say that in our study there was a beneficial effect.

It has already been shown in patients taking ACE inhibitor that chronic posttransplant failure was ameliorated only in patients with proteinuria reduction and has been concluded that it is very unlikely for the progressive nature of the disease to be altered if the proteinuria is unresponsive to ACE inhibitors[30]. It is very early to draw any cocnclusion for our proteinuric patients taking AT1RA. The use of ACE inhibitors has been connected with drug withdrawal in 17% of the included patients because of serum creatinine elevation over 20% above baseline and 6% because of other side effects (cough, exanthema)[30]. None of our patients had cough or presented exanthema and nobody stopped taking AT1RA. The number of antihypertensive drugs needed decreased significantly during the six month treatment but the levels of systolic and diastolic blood pressure did not present difference during the follow up period before and after AT1RA use. This finding suggests that the proteinuria reduction is peripheral blood pressure independent.

The mechanism by which AT1RA reduce Hb levels has already been analysed and our findings show that there is ss decrease of Hb in agreement with our previous studies. Also cyclosporine levels did not change as it was expected[21,22].

Having in mind that proteinuria is an independent risk factor for chronic allograft nephropathy with a relative risk of 1.42[3], the fact that in studies on the effect of antihypertensive drugs on the rate of progression of non transplant

renal failure the antiproteinuric effect is often used as a surrogate marker[31] and the results of our study we can conclude that the AT1RA treatment reduces ss proteinuria in renal transplant recipients, controls efficiently arterial blood pressure, does not change serum creatinine levels in this cohort of patients and therefore retards the interstitial lesion expansion reducing the relative risk for graft loss. Our results combined with the knowledge that the administration of an angiotensin II receptor antagonist in a normotensive rat model with proliferative nephritis caused significant reduction of proteinuria[32] and that combined therapy of an ACE inhibitor and an angiotensin II receptor antagonist totally prevented proteinuria in rats and preserved renal morphology[33] we should be justified to try in the future a combined treatment of proteinuria with AT1RA and ACE inhibitor in patients resistant to treatment with an AT1RA alone.

ΠΕΡΙΛΗΨΗ

Γ. Βέργουλας, Γρ. Μυσερλής, Β. Παπανικολάου, Φ. Καρασαββίδου, Μ. Λεοντσίνη, Δ. Γάκης, Α. Παντζάκη, Ε. Ατματζίδης, Δ. Τακούδας, Α. Αντωνιάδης. **Οι ανταγωνιστές των υποδοχέων τύπου 1 της αγγειοτασίνης ΙΙ ελαττώνουν την λευκωματουρία των υπερτασικών λιπτών νεφρικού μοσχεύματος.** Ιπποκράτεια 2001, 5 (4): 165-171

Ο σκοπός της μελέτης αυτής ήταν η διερεύνηση της ασφάλειας και της αποτελεσματικότητας των ανταγωνιστών των υποδοχέων τύπου 1 της αγγειοτασίνης ΙΙ (ΑΤ1RA) σε υπερτασικούς λήπτες νεφρικού μοσχεύματος με λευκωματουρία. Στη μελέτη περιελήφθησαν δεκαοκτώ ασθενείς με υπέρταση και λευκωματουρία . Οι ασθενείς αυτοί (14 άνδρες) με μέση ηλικία 48 έτη (διακύμανση 31 – 64 έτη) έλαβαν για την αντιμετώπιση της υπέρτασής τους ανταγωνιστές των υποδοχέων τύπου 1 της αγγειοτασίνης ΙΙ (11 λοζαρτάνη και 7 βαλσαρτάνη) 4,33 έτη μετά τη νεφρική μεταμόσχευση (διακύμανση 0,5 – 11 έτη). Όλοι είχαν παρακολούθηση 6 μηνών πριν και μετά την χορήγηση των ανταγωνιστών της αγγειοτασίνης. Η συστολική και η διαστολική πίεση του αρτηριακού αίματος, η κρεατινίνη ορού, και η Hb καταγράφηκαν ανά δίμηνο πριν και μετά τη χορήγηση των ΑΤ1RA. Η λευκωματουρία, ο αριθμός των αντιυπερτασικών παραγόντων και τα επίπεδα της κυκλοσπορίνης καταγράφηκαν κατά την έναρξη της θεραπείας με ΑΤ1RA και έξι μήνες αργότερα. Για την στατιστική ανάλυση χρησιμοποιήθηκε ANOVA για επαναλαμβανόμενες μετρήσεις τιμών και t test για ζεύγη τιμών.

Η SBP/DBP ήταν 143.12±14.00/90.31± 10.07 mmHg, 146.87±10.62/ 90.00 ±7.30 mmHg, 148.12±12.63/93.75±8.85 mm Hg, και 146.25± 13.96/ 86.25±5.91 mmHg 6,4,2 και 0 μήνες πριν την χορήγηση ΑΤ1RA αντίστοιχα (p:NS) και 139.33±14.8/85.33±5.49 mmHg, 143.66± 17.05/ 86.00±8.06 mmHg και 142.33± 10.99/ 87.33±8.42 mmHg 2, 4 και 6 μήνες μετά την έναρξη χορήγησης ΑΤ1RA αντίστοιχα (p:NS). Η Scr ήταν 1.53±0.55 mg/dl, 1.61±0.70 mg/dl, 1.66±0.70 mg/dl και 1.68±0.71 mg/dl 6, 4, 2 και 0 μήνες πριν την έναρξη χορήγησης ΑΤ1RA αντίστοιχα (p:NS) και 1.78±0.80 mg/dl, 1.84±0.87 mg/dl και 1.82± 0.94 mg/dl 2, 4 και 6 μήνες μετά την έναρξη των ΑΤ1RA αντίστοιχα (p:NS). Η Hb ήταν 12.80±2.11 g/dl, 12.57±1.78 g/dl 12.73 ± 1.80 g/dl και 12.26±2.09 g/dl 6,4,2 και 0 μήνες πριν την έναρξη των ΑΤ1RA αντίστοιχα και 12.10±1.69 g/dl, 11.48±1.59 g/dl και 11.55±1.62 g/dl 2, 4 και 6 μήνες μετά την έναρξη των ΑΤ1RA αντίστοιχα (p:0.005). Η Pr ήταν 0.76±0.77 g/dl g/24 h πριν και 0.61±0.63 g/24 h μετά την έναρξη των ΑΤ1RA (p:0.024). Ο αριθμός των αντιυπερτασικών φαρμάκων ήταν 2.27±0.89 και 1.83±0.85 πριν και έξι μήνες μετά την έναρξη των ΑΤ1RA (p:0.007). Τα επίπεδα της CsA ήταν 83.75±42.22 και 70.24±40.16 ng/L πριν και μετά την θεραπεία με ΑΤ1RA (p:NS).

Οι ΑΤ1RA ελαττώνουν στατιστικά σημαντικά τη λευκωματουρία υπερτασικών που έχουν λάβει νεφρικό μόσχευμα, ελέγχουν επαρκώς την αρτηριακή τους πίεση, ελαττώνουν τον αριθμό των αντιυπερτασικών που απαιτούνται, δεν προκαλούν επιδείνωση της λειτουργικότητας του νεφρικού μοσχεύματος όπως φαίνεται από τα επίπεδα της κρεατινίνης ορού, και προκαλούν μια μικρή αλλά στατιστικά σημαντική πτώση της Hb του αίματος.

REFERENCES

1. Paul LC. Chronic allograft nephropathy. Kidney Int 1999;56:783-793
2. Barnas U, Schmidt A, Haas M, et al. Parameters associated with chronic renal transplant failure. Nephrol Dial Transplant 1997;12(Suppl 2):82-85
3. Massy ZA, Guijarro C, Wiederkehr MR, Ma JZ, Kasiske BL. Chronic renal allograft rejection: Immunologic and nonimmunologic risk factors. Kidney Int 1996;49:518-524

4. Oberbauer R, Haas M, Regele H, Barnas U, Schmit A, Mayer G. Glomerular permselectivity in proteinuric patients after kidney transplantation. J Clin Invest 1995;96:22-29
5. Goode NP, Shires M, Davison AM. The glomerular basement membrane charge-selectivity barrier: an oversimplified concept? Nephrol Dial Transplant 1996;11:1714-1716
6. Remmuzzi G, Ruggenetti P, Benigni A. Understanding the nature of renal disease progression. Kidney Int 1997;51:2-15
7. Bruzzi I, Benigni A, Remmuzi G. Role of increased glomerular protein traffic in the progression of renal failure. Kidney Int 1997;52(Suppl 62):S29-S31
8. Kuroiwa T, Schlimgen R, Illei GG, McIness IB, Boumpas DT. Distinct T cell/ renal tubular epithelial cell interactions define differential chemokine production: implications for tubulointerstitial injury in chronic glomerulonephritis. J Immunol 2000;164:3323-3329
9. Frasca L, Marelli-Berg F, Immami N, et al. Interferon-gamma-treated renal tubular epithelial cells induce allospecific tolerance. Kidney Int 1998;53: 679-689
10. Deckers JG, Daha MR, Van der Kooij SW, Van der Woude FJ. Epithelial- and endothelial-cell specificity of renal graft infiltrating cells. Clin Transplant 1998;12:285-291
11. Bohle A, Wehrmann M, Mackensen – Haem S, et al. Pathogenesis of chronic renal failure in primary glomerulopathies. Nephrol Dial Transplant 1994;9(Suppl 3):4-12
12. Rosenkranz AR, Mayer G. Proteinuria in the transplanted patient. Nephrol Dial Transplant 2000;15:1290-1292
13. Cheng QL, Chen XM, Li F, Lin HL, Ye YZ, Fu B. Effects of ICAM-1 antisense oligonucleotide on the tubulointrstitium in mice with unilateral ureteral obstruction. Kidney Int 2000;57:183-190
14. Ong ACM, Jowett TP, Frirth JD, Burton S, Kitamura M, Fine LG. A new paracrine loop implicated in human tubular-interstitial fibrosis: Tubular-derived endothelins modulate renal interstitial fibroblasts function. J Am Soc Nephrol 1993;4:473 abstract
15. Achmad T, Rao G. Chemotaxis of human blood moncytes towards endothelin-1 and the influence of calcium channel blockers. Biochem Biopsy Res Commun 1992;189:994-1000
16. Jafar TH, Stark PC, Schmid CH, et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. Kidney Int 2001;60:1131-1140
17. Wolf G. Angiotensin II: a pivotal factor in the progression of renal diseases. Nephrol Dial Transplant 1999;14(Suppl 1):42-44
18. Bombas A, Stein-Oakley AN, Baxter K, Thomson NM, Jablonski P. Development of injury in a rat model of chronic allograft rejection: effect of dietary protein restriction. Transplant Int 1999;12:18-26
19. Botchhardt K, Haas M, Yilmaz N, et al. Low dose angiotensin converting enzyme inhibition and glomerular permselectivity in renal transplant recipients. Kidney Int 1997;52:1622-1825
20. Grekas D, Dioudis C, Kalevrosoglou I, et al. Management of moderate to severe hypertension and proteinuria by nifedipine retard and perindopril after renal transplantation. Clin Nephrol 1995;44:299-302
21. Vergoulas G, Miserlis Gr, Trellopoulos G, Antoniadis A. Evaluation of losartan in patients with renal transplantation. Hippokratia 2000,4:67-72
22. Vergoulas G, Miserlis Gr, Gakis D, Atmatzidis E, Antoniadis A. The use of valsartan in hypertensive renal transplant recipients. Hippokratia 2001;5: 61-68
23. Burton CJ, Harris KPG. The role of proteinuria in the progression of chronic renal failure. Am J Kidney Dis 1996;27:765-775
24. Remuzzi G. Nephropathic nature of proteinuria. Cur Opin Nephrol Hypertens 1999;8:655-663
25. Barnas U, Schmidt A, Haas, Oberbauer R, Mayer G. The effects of prolonged angiotensin – converting enzyme inhibition on excretory kidney function and proteinuria in renal allograft recipients with chronic progressive transplant failure. Nephrol Dial Transplant 1996;11:1822-1824
26. Makenzie H, Ots M, Ziaj F, et al. Angiotensin receptor antagonists in experimental models of chronic renal failure. Kidney Int 1997;52(Suppl 63): S140-S143
27. Plum J, Buenten B, Nemeth R, Grabensee B. The effects of the angiotensin II antagonist valsartan on blood pressure, proteinuria and renal hemodynamics in patients with chronic renal failure and hypertension. J Am Soc Nephrol 1998;9:2223-2234
28. Del Castillo D, Campistol JM, Guirado L, et al. Efficacy and safety of losartan in the treatment of hypertension in renal transplant recipients. Kidney Int 1998, 54(Suppl 68):S135-S139
29. Modena FM, Cohen RA, Salahudeen AK, Najarian JS, Matas AJ, Rosenberg ME. Progression of kidney disease in chronic renal transplant rejection. Transplantation 1991;52:239-244
30. Oppenheimer F, Flores R, Cofan F, et al. Treatment with angiotensin converting enzyme inhibitors in renal transplantation with proteinuria. Transplant Proc 1995;27:2235-2236
31. The GISEN Group. Randomized placebo-controlled trial on the effect of ramipril in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 1997;349:1857-1863
32. Gomez-Carre D, Largo R, Liu XH, An orally active ETa/ETb receptor antagonist ameliorates proteinuria and glomerular lesions in rats with proliferative nephritis. Kidney Int 1996;50:962-972
33. Liu XH, Oldroyd S, Abbate M, et al. Combined administration of ACE inhibitor and angiotensin II receptor antagonist normalizes excessive renal endothelin-1 gene expression in a rats with passive Heymann nephritis. J Am Soc Nephrol 1995;6:874 (abstract)

Αλληλογραφία
Γ. Βέργουλας,
Αλκμήνης 53
542 49 Θεσσαλονίκη
Τηλ. & Fax 0310 302311
email: geover@otenet.gr

Corresponding author
Vergoulas G,
53 Alkminis str
542 49 Thessaloniki
Greece
Tel & Fax +30 310 992886
email: geover@otenet.gr