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clinical nephrology

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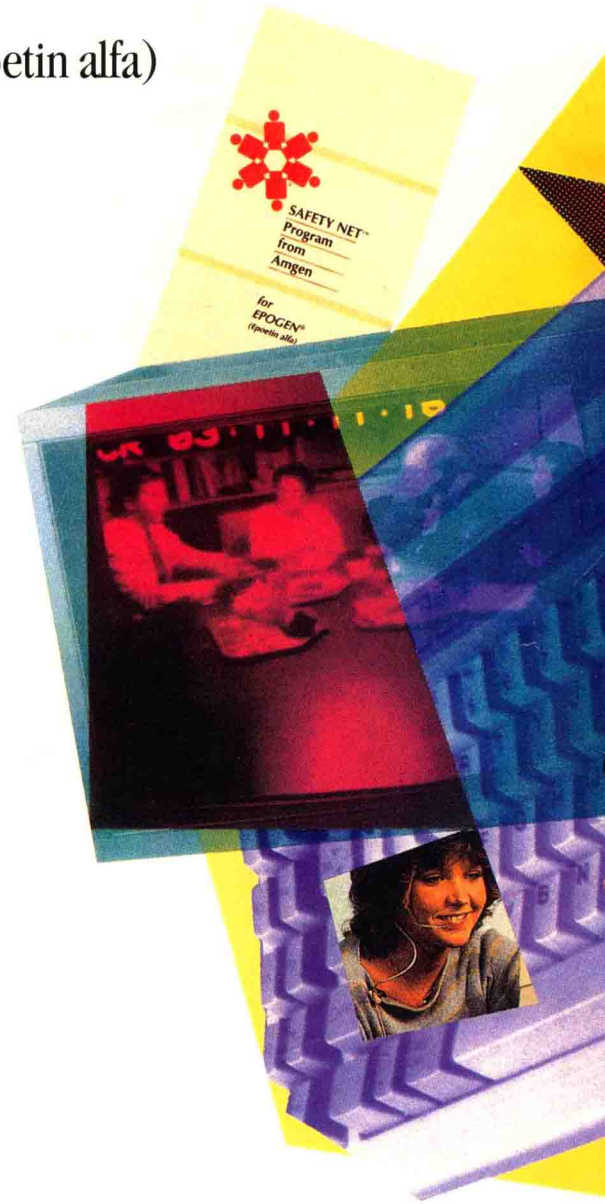

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Unique dual mechanism of action

Controls hypertension through a combination of mild diuresis and vasodilatation[1,2]

Gradually reduces both systolic and diastolic blood pressures[3,4]

Well-tolerated hypertension control

Low patient dropout rate due to favorable side-effect profile and convenient once-daily dosing[5]

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LOZOL® INDAPAMIDE 2.5mg TABLETS

Please see brief summary of prescribing information below.

LOZOL® (indapamide) **2.5 mg tablets**
BRIEF SUMMARY

INDICATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.
Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with the use of recommended doses of indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (**see ADVERSE REACTIONS, hypokalemia**), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical trials, adverse reactions with $\geq$ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; $<$ 5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Hypokalemia with concomitant clinical signs or symptoms occurred in 3% of patients receiving indapamide 2.5 mg q.d. and 7% of patients receiving indapamide 5 mg q.d. In long-term controlled clinical trials comparing the hypokalemic effects of daily doses of indapamide and hydrochlorothiazide, however, 47% of patients receiving indapamide 2.5 mg, 72% of patients receiving indapamide 5 mg, and 44% of patients receiving hydrochlorothiazide 50 mg had at least one potassium value (out of a total of 11 taken during the study) below 3.5 mEq/L. On the indapamide 2.5 mg group, over 50% of those patients returned to normal serum potassium values without intervention. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at room temperature. Avoid excessive heat.
Dispense in tight containers as defined in USP.
See product circular for full prescribing information. Revised: March 1992

References: 1. **Campbell DB:** The possible mode of action of indapamide: A review. *Curr Med Res Opin* 1983;8(Suppl 3):9-24. 2. **Wilson PR,** Kem DC: Indapamide. In: Messerli FH, ed. *Cardiovascular Drug Therapy*. Philadelphia: W.B. Saunders Co. 1990;348-356. 3. **Mimran A,** Zambrowski JJ, Coppolani T: The antihypertensive action of indapamide: Results of a French multicentre study of 2,184 ambulant patients. *Postgrad Med J* 1981;57(Suppl 2):60-63. 4. **Data on file,** Rhône-Poulenc Rorer Pharmaceuticals Inc. 5. **Abbou C-B:** The efficacy and tolerance of indapamide in essential hypertension: A multi-centre study in 981 patients. *Curr Med Res Opin* 1985;9(7):494-499. 6. **Beling S,** Vukovich RA, Neiss ES, et al: Long-term experience with indapamide. *Am Heart J* 1983;106(1, Part 2):258-262. 7. **Scalabrino A,** Galeone F, Giuntoli F, et al: Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res* 1984;35(1):17-22.
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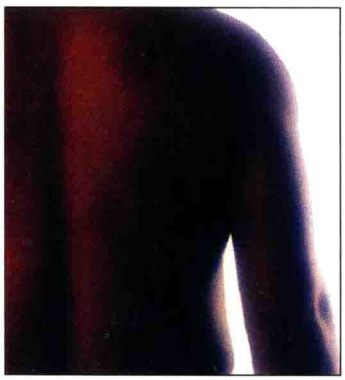
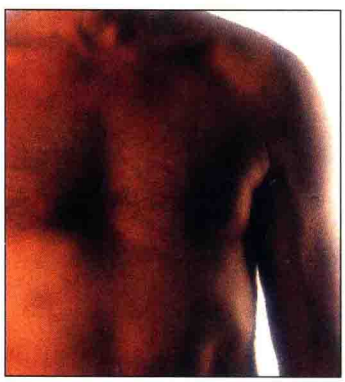
Because coexisting conditions often complicate hypertension...

DynaCirc® puts their safety first.
(isradipine)



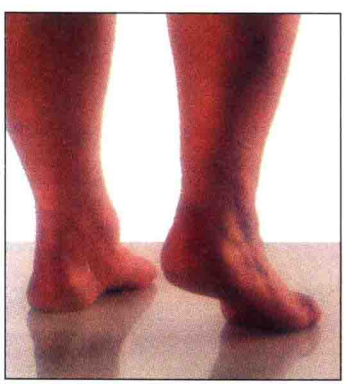
Facilitates renal function.

- No clinically significant change in serum creatinine[1,2] or creatinine clearance[1,3]
- No clinically significant effect on glomerular filtration rate[3-6]
- Maintains or decreases filtration fraction[1,3,6]



Maintains cardiac performance.

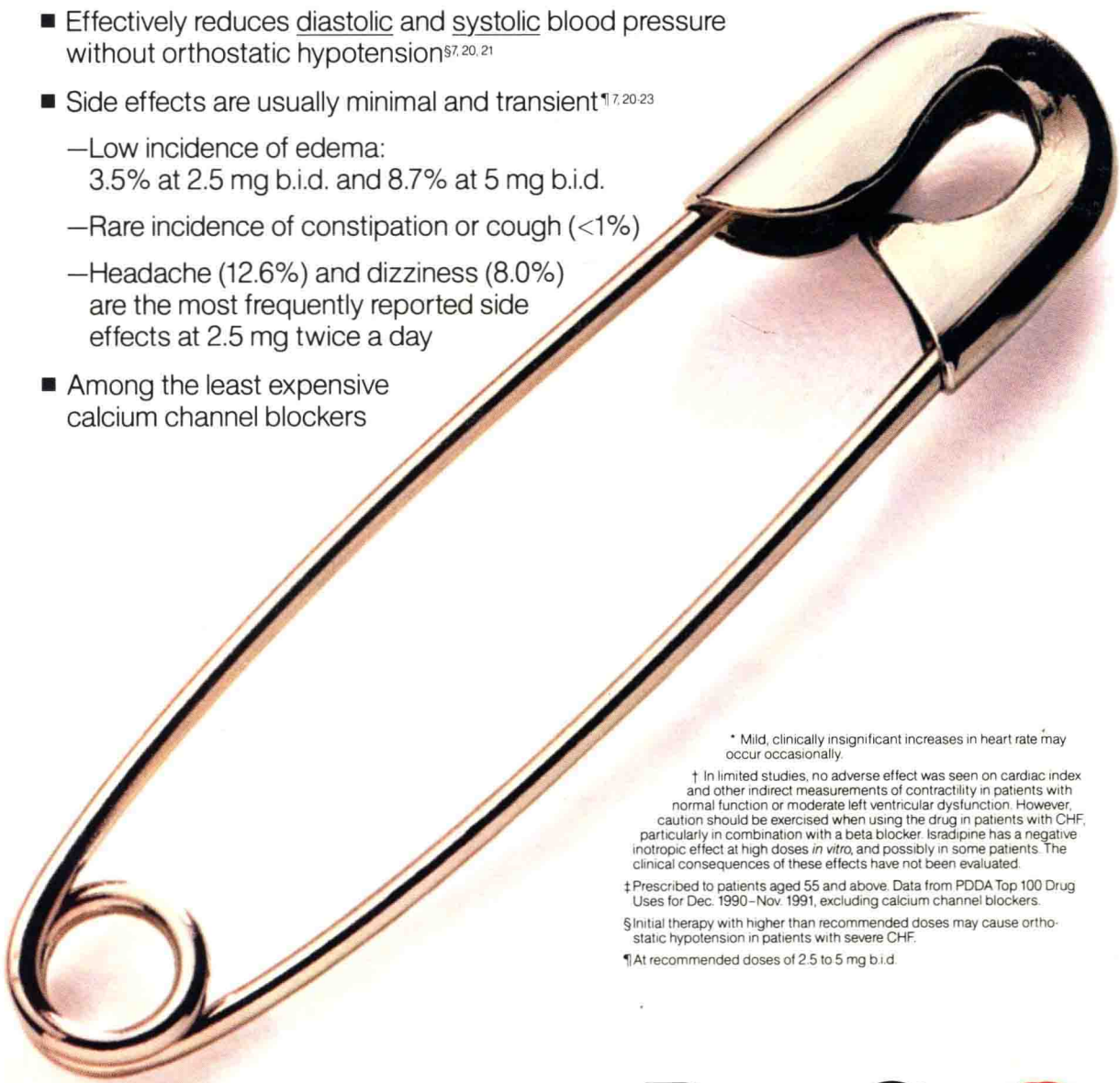
- No significant effect on heart rate*[7-10]
- No adverse effect on cardiac conduction[11,12] or contractility†[3,10,13-15]
- No alteration of digoxin clearance[16]



Does not compromise metabolic parameters.

- No clinically significant effect on serum glucose metabolism[17]
- No effect on glucose tolerance, insulin secretion or insulin action in NIDDM patients[17]
- No clinically significant effect on lipid metabolism[18,19]

- No known contraindications except for hypersensitivity to DynaCirc
- No significant interactions with the 20 most-commonly prescribed drugs‡
- Effectively reduces diastolic and systolic blood pressure without orthostatic hypotension§[7,20,21]
- Side effects are usually minimal and transient¶[7,20-23]
  - —Low incidence of edema: 3.5% at 2.5 mg b.i.d. and 8.7% at 5 mg b.i.d.
  - —Rare incidence of constipation or cough (<1%)
  - —Headache (12.6%) and dizziness (8.0%) are the most frequently reported side effects at 2.5 mg twice a day
- Among the least expensive calcium channel blockers



* Mild, clinically insignificant increases in heart rate may occur occasionally.

† In limited studies, no adverse effect was seen on cardiac index and other indirect measurements of contractility in patients with normal function or moderate left ventricular dysfunction. However, caution should be exercised when using the drug in patients with CHF, particularly in combination with a beta blocker. Isradipine has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. The clinical consequences of these effects have not been evaluated.

‡ Prescribed to patients aged 55 and above. Data from PDDA Top 100 Drug Uses for Dec. 1990–Nov. 1991, excluding calcium channel blockers.

§ Initial therapy with higher than recommended doses may cause orthostatic hypotension in patients with severe CHF.

¶ At recommended doses of 2.5 to 5 mg b.i.d.

DynaCirc®
2.5 mg capsules (isradipine) 5 mg capsules
For Safety's Sake™

Please see following page for brief summary of full Prescribing Information.

BRIEF SUMMARY
Please see package insert for full prescribing information.

DYNACIRC® (isradipine) CAPSULES

INDICATION

DynaCirc® (isradipine) is indicated in the management of hypertension. It may be used alone or concurrently with thiazide-type diuretics.

CONTRAINDICATIONS

DynaCirc® is contraindicated in individuals who have shown hypersensitivity to any of the ingredients in the formulation.

WARNINGS

None.

PRECAUTIONS

General: *Blood Pressure:* Because DynaCirc® decreases peripheral resistance, like other calcium blockers DynaCirc® may occasionally produce symptomatic hypotension. However, symptoms like syncope and severe dizziness have rarely been reported in hypertensive patients administered DynaCirc®, particularly at the initial recommended doses. *Use in Patients with Congestive Heart Failure:* Although acute hemodynamic studies in patients with congestive heart failure have shown that DynaCirc® reduced afterload without impairing myocardial contractility, it has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker. **Drug Interactions:** *Nitroglycerin:* DynaCirc® has been safely coadministered with nitroglycerin. *Hydrochlorothiazide:* A study in normal healthy volunteers has shown that concomitant administration of DynaCirc® and hydrochlorothiazide does not result in altered pharmacokinetics of either drug. In a study in hypertensive patients, addition of isradipine to existing hydrochlorothiazide therapy did not result in any unexpected adverse effects, and isradipine had an additional antihypertensive effect.

Propranolol: In a single dose study in normal volunteers coadministration of propranolol had a small effect on the rate but no effect on the extent of isradipine bioavailability. Coadministration of DynaCirc® resulted in significant increases in AUC (27%) and C_{max} (58%) and decreases in t_{max} (23%) of propranolol. *Digoxin:* The concomitant administration of DynaCirc® and digoxin in a single-dose pharmacokinetic study did not affect renal, nonrenal and total body clearance of digoxin. *Fentanyl Anesthesia:* Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta blocker and a calcium channel blocker. Even though such interactions have not been seen in clinical studies with DynaCirc®, an increased volume of circulating fluids might be required if such an interaction were to occur. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Treatment of male rats for 2 years with 2.5, 12.5, or 62.5 mg/kg/day isradipine admixed with the diet resulted in dose dependent increases in the incidence of benign Leydig cell tumors and testicular hyperplasia relative to untreated control animals. A comparable endocrine effect was not evident in male patients receiving therapeutic doses of the drug on a chronic basis. Treatment of mice for two years with 2.5, 15, or 80 mg/kg/day isradipine in the diet showed no evidence of oncogenicity. There was no evidence of mutagenic potential based on the results of a battery of mutagenicity tests. No effect on fertility was observed in male and female rats. **Pregnancy:** *Pregnancy Category C:* There are no adequate and well controlled studies in pregnant women. DynaCirc® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether DynaCirc® is excreted in human milk. A decision should be made as to whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness have not been established in children.

ADVERSE REACTIONS

The adverse reaction rates given below are principally based on controlled hypertension studies, but rarer serious events are derived from all exposures to DynaCirc®, including foreign marketing experience. Most adverse reactions were mild and related to the vasodilatory effects of DynaCirc® (dizziness, edema, palpitations, flushing, tachycardia), and many were transient. About 5% of isradipine patients left studies prematurely because of adverse reactions (vs. 3% of placebo patients and 6% of active control patients), principally due to headache, edema, dizziness, palpitations, and gastrointestinal disturbances. The following adverse reactions have been reported by 1% or greater of patients receiving DynaCirc® at any dose (N=934): headache (13.7%), dizziness (7.3%), edema (7.2%), palpitations (4.0%), fatigue (3.9%), flushing (2.6%), chest pain (2.4%), nausea (1.8%), dyspnea (1.8%), abdominal discomfort (1.7%), tachycardia (1.5%), rash (1.5%), pollakiuria (1.5%), weakness (1.2%), vomiting (1.1%), diarrhea (1.1%). The following adverse events were reported in 0.5-1% of the isradipine-treated patients in hypertension studies, or are rare, but more serious events from this and other data sources, including postmarketing exposure, are shown in italics. The relationship of these adverse events to isradipine administration is uncertain. **Skin:** pruritus, *urticaria.* **Musculoskeletal:** cramps of legs/feet. **Respiratory:** cough. **Cardiovascular:** shortness of breath, hypotension, *atrial fibrillation, ventricular fibrillation, myocardial infarction, heart failure.* **Gastrointestinal:** abdominal discomfort, constipation, diarrhea. **Urogenital:** nocturia. **Nervous System:** drowsiness, insomnia, lethargy, nervousness, impotence, decreased libido, depression, *syncope, paresthesia* (which includes numbness and tingling), *transient ischemic attack, stroke.* **Autonomic:** hyperhidrosis, visual disturbance, dry mouth, numbness. **Miscellaneous:** throat discomfort, *leukopenia, elevated liver function tests.*

[DECEMBER 31, 1990 DYN-Z2]

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Soluble interleukin-2 receptor levels in lupus nephritis

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[3] *Rheumatology Division, Department of Medicine, and*
[4] *Department of Pathology, Montefiore Medical Center of the Albert Einstein College of Medicine, Bronx, New York, USA*

Abstract. Soluble interleukin-2 receptor (IL-2R) levels were measured and correlated prospectively with clinical, histologic and serologic findings over a 9-month period in 62 lupus patients. Initially, 39 patients had clinical nephritis and 23 patients did not have nephritis. The 62 lupus patients has significantly higher IL-2R than 15 normal controls, most of this difference attributable to patients with nephritis. During lupus nephritis flare 9 of 10 patients showed significant elevations of IL-2R while only 6 of the 10 patients showed either elevation of anti-DNA antibody or decrease in CH_{50}. During disease remission or stable clinical activity changes in IL-2R levels paralleled changes in anti-DNA antibody and CH_{50}. Nephritis patients with cellular proliferative histology had significantly higher IL-2R levels than those with membranous or mesangial nephropathy. IL-2R correlated strongly with histologic activity and chronicity indices, IgG and C3 deposition whereas anti-DNA antibody and CH_{50} levels did not. IL-2R levels did not correlate with serum creatinine suggesting that elevations of IL-2R were not simply due to decreased clearance. These observations suggest that serum IL-2R level is a useful marker of disease activity in lupus nephritis and may serve as a helpful adjunct in management of this disorder.

Key words: systemic lupus erythematosus – lupus nephritis – interleukin-2 receptor

Introduction

Systemic lupus erythematosus (SLE) is characterized by multiple B- and T-lymphocyte abnormalities. Autoantibody production is a hallmark of the disease. Immune complex deposition and subsequent activation of the complement system are involved in disease pathogenesis [Lloyd and Schur 1981]. Measurements of serum anti-DNA antibody levels, immune complexes and complement components are the serologic tests most frequently used to assess activity in SLE, but these tests function imperfectly in this role.

Recently it has been found that activated T- and B-cells release both interleukin-2 and a soluble form of the interleukin-2 receptor (IL-2R) [Rubin et al. 1985]. The serum IL-2R level thus has been used as a marker for disease activity in a number of conditions associated with T- and B-cell activation including collagen vascular disease, infections, organ transplantation and neoplastic disease [Campen et al. 1988, Symons et al. 1988, Semenzato et al. 1988, Rubin and Nelson 1990, Wolf and Brelsford 1988, Tokano et al. 1989, Waldmann 1990, Ter Borg et al. 1990, Degiannis et al. 1990, Senitzer et al. 1991]. Serum IL-2R levels have been correlated with global disease activity index in SLE and with various serologic parameters [Campen et al. 1988, Laitman et al. 1989, Lloyd and Schur 1981, McCune et al. 1988]. To date, IL-2R levels have not been evaluated more specifically in relation to clinical and histologic changes in lupus nephritis.

Lupus nephritis (LN) is characterized by multiple intermittent clinical flares of disease activity which often cause irreversible damage to the kidneys [Steinberg 1986, McCune et al. 1988, Laitman et al. 1989]. Periods when there are no clinical signs of active glomerulonephritis may nonetheless be associated with progressive immunologic damage to the remaining nephrons [Steinberg 1986]. Therefore it would be advantageous to anticipate disease activity by serologic tests to better adjust immunosuppressive therapy. However, there is not always a clear correlation between abnormal levels of anti-DNA antibody or complement and clinical lupus nephritis activity [Steinberg 1986, Schur 1987]. In this regard, a more

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direct marker of lymphocyte activation such as serum levels or soluble IL-2R may be a useful adjunctive test. The purpose of our study was to determine whether serum IL-2R is a sensitive marker for disease activity in LN.

Methods

Patients

Sixty-two patients (57 females, 5 males) were randomly selected from a total of 157 patients attending the Lupus Clinic at Montefiore Medical Center. All were diagnosed as having SLE according to standard criteria [Tan et al. 1982]. Their mean age at the start of the study was 32.6 ± 4 years. Diagnosis of SLE was made 4.7 ± 0.6 years prior to entry into the study. Patients were followed prospectively up to 9 months. No patient included in this study had extrarenal lupus flare without concurrent nephritis flare. Patients whose lupus activity was limited to severe extrarenal disease (i.e. cerebritis) were excluded in this study. Cases of documented sepsis were also excluded from this study.

Assessment of nephritis activity

Lupus nephritis activity was evaluated at each clinic visit and at least once during any hospital admission. Active nephritis was defined by the following criteria, modified slightly from Cameron et al. [1976]: 24-hour urine protein > 200 mg; urinalysis showing at least 5 red blood or white blood cells per high power field in the absence of infection; red cell casts; rise in serum creatinine above baseline of at least 35 SI (0.4 mg/dl) without other apparent cause.

Changes in lupus nephritis activity were noted. A renal flare was defined by at least two of the following criteria: rise in serum creatinine of ≥ 35 SI (0.4 mg/dl) sustained over 3 months; doubling of proteinuria or progression from non-nephrotic to nephrotic range (3.5 g/day); new development of hematuria or pyuria (≥ 5 cells/high power field) with negative urine culture; appearance of red blood cell casts; new onset hypertension, defined as > 140/90 mmHg. A remission of lupus nephritis was defined as including all of the following: at least 50% reduction in urinary protein excretion or decrease from nephrotic to non-nephrotic range; fall in serum creatinine of > 35 SI (0.4 mg/dl) sustained for at least one month; resolution of hematuria, pyuria or red cell casts.

Renal biopsy was performed in 24 of the 62 patients. Tissue was studied by light, immunofluorescence and electron microscopy. IL-2R levels were measured within 24 hours of the biopsy. World Health Organization (WHO) classification as well as activity and chronicity indices were determined as previously described [Laitman et al. 1989]. Extent of immunoglobulin deposition was semiquantitatively scored using a scale of 0 to 3+. All histologic evaluations were performed by two separate observers who were blinded to clinical and serologic data.

Table 1 Patient groups

	Lupus nephritis n = 39	No nephritis n = 23	Total n = 62
Age (yr)	32.3 ± 5	33.2 ± 7	32.6 ± 4
Sex (F/M)	34/5	23/0	57/5
SLE duration (yr)	4.1 ± 0.7	5.7 ± 1.0	4.7 ± 0.6

Table 2 Comparison of nephritis with no nephritis

	LN (+) n = 39	LN (−) n = 23	P <
IL-2R (u/ml)	1097 ± 83	469 ± 46	0.0001
CH_{50} (u/ml)	144 ± 11	177 ± 11	NS
Anti-DNA (iu/ml)	769 ± 110	389 ± 72	0.02
Serum creatinine (SI)	114.9 ± 12.4	77.8 ± 2.6	0.02
Urine protein (g/d)	2.8 ± 0.5	0.01 ± 0.006	0.0001

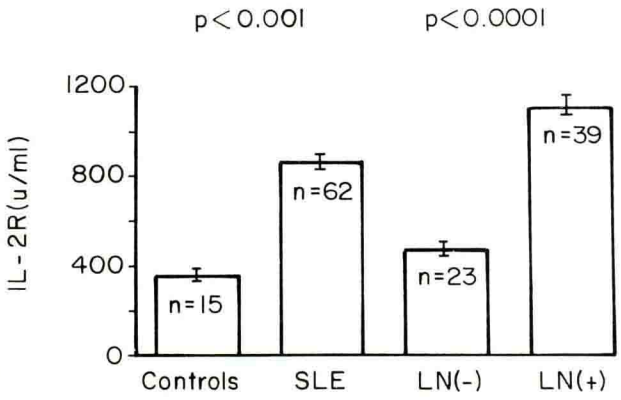

Fig. 1 Serum IL-2R levels in controls, the total group of SLE patients, and SLE patients divided according to the presence (+) or absence (−) of lupus nephritis (LN)

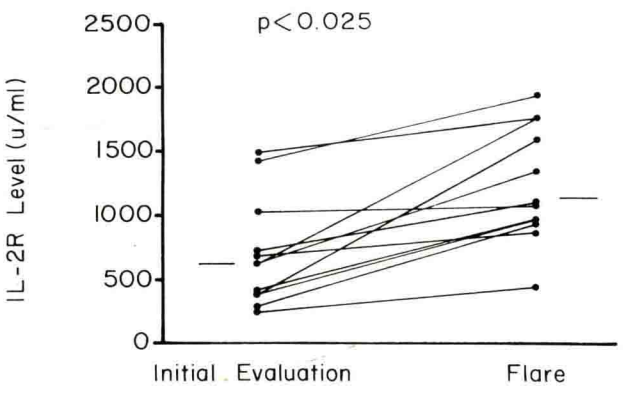

Fig. 2 Serum IL-2R levels at initial evaluation and at time of renal disease flare, in ten patients with systemic lupus. Horizontal bars represent the means

Blood samples

Blood samples were allowed to clot and serum separated after centrifugation was stored at −70° C until assayed. The stability of IL-2R under these conditions has been documented [Campen et al. 1988].

Study design

During the 9-month study period, serum samples were collected at each clinic visit for IL-2R, routine chemistries, anti-DNA antibodies and complement (CH_{50}). At the same visit routine urinalysis, urine for protein/creatinine ratio or 24-hr urine collections and blood pressure measurement were obtained. Patients underwent percutaneous renal biopsy for clinical indications such as persistence of clinical nephritis or nephrotic syndrome on steroid therapy alone, if there was abrupt deterioration of renal function or for persistent (> 3 months) hypocomplementemia. However, no biopsies were performed for hypocomplementemia alone. Patients were treated for major disease exacerbations with prednisone up to 2 mg/kg/d and azathioprine 2.5 mg/kg/d for a maximum of six months depending on clinical response until the serum CH_{50} normalized. After clinical remission or maintenance of a normal CH_{50} level for at least one month prednisone was tapered by 10% decrements every 10 days until a dose of 5 mg/d was reached. Patients not responding to this regimen received cyclophosphamide 0.75 g/m^2 of body surface monthly by intravenous infusion along with oral prednisone 0.5 mg/kg/d for six months. After six months cyclophosphamide was given every three months and oral prednisone tapered as previously described.

Assays

Interleukin-2 receptor levels were determined using a double monoclonal antibody enzyme immunoassay (T cell Sciences, Cambridge, MA). Briefly, 96-well microtiter plates were coated with the first anti-IL-2R monoclonal antibody (Anti-Tac), and incubated with serum samples for two hours at 37° C, then washed to remove any unbound component. A second monoclonal anti-IL-2R antibody, recognizing a separate epitope, was conjugated with horse radish peroxidase and then added to the wells and again incubated for two hours at 37° C. The samples were washed, substrate (O-phenylenediamine) added and then they were incubated for thirty minutes at room temperature. Absorbance at 490 nm was determinded using a Dynatech ELISA reader (Alexandra, Virginia). Absorbance readings were converted to Units/ml (U/ml) by comparison to the standard curve run with each assay. Standards (5) supplied by the manufacturer ranged from 0 to 1600 U/ml. In addition, two controls were included in each assay (high and low ends of the curve). Patient samples were run without dilution, or at 1/10 if necessary. Serum IL-2R levels are expressed in units per milliliter. Total hemolytic complement activity (CH_{50}) (normal > 150 u/ml) was quantitated in serum stored at −70° C using the method of Kent and Fife [1963]. In this assay the amount of serum required for 50% hemolysis of an aliquot of sheep erythrocytes coated with a rabbit hemolysin (Sigma Co., St. Louis, Missouri) is proportional to the level of CH_{50} and is dependent on the presence of all of the components in the classical complement fixation pathway. Anti-DNA antibody titers (normal <450 iu/ml) were determined by a solid phase ELISA method (Sigma Co., St. Louis, Missouri).

Statistical analysis

Unpaired t-test was used for comparison between groups. Paired t-test was used to compare changes in parameters in the same group. Linear regression was used to analyze correlations. The general formula used was $y = mx + b$. For comparing IL-2R levels with activity index, the equation $y = 0.01x - 0.62$ was used. Comparing IL-2R with chronicity index, the equation $y = 0.001x - 0.99$ was used. The equation $y = 0.38x + 1.26$ was used to compare activity index with chronicity index. P values of 0.05 or less were considered significant.

Results

The 62 patients were divided into two groups according to the presence or absence of clinical nephritis at the time of initial evaluation for this study. Extra-renal SLE activity was not a factor in assignment to these two groups. There were 39 patients with nephritis and 23 initially without nephritis (Table 1).

IL-2R levels in 15 normal controls were compared with our lupus patients (Figure 1). The total group of SLE patients had significantly higher IL-2R levels than controls. Most of this elevation could be attributed to patients with nephritis, whose IL-2R levels were significantly higher than patients without nephritis. Extra-renal manifestations such as fever, rash, arthralgias, while not specifically quantitated, were present only in patients with nephritis. There was no significant difference in IL-2R levels between controls versus SLE patients without nephritis. The mean IL-2R level of 375 u/ml for the control group is similar to normal values reported by others [Campen et al. 1988, Ter Borg et al. 1990].

Nephritis patients had higher IL-2R and anti-DNA antibody levels but similar CH_{50} levels when compared to SLE patients without nephritis (Table 2). Mean daily steroid dose was higher in the nephritis patients (30 ± 4.4 vs 12 ± 3.2 mg/d, $p < 0.001$) reflecting more active disease in these patients.

Twenty-six patients had stable activity over the study period. This included some of the patients without clinical nephritis on initial evaluation as well as patients with nephritis whose clinical parameters did not change. In all of these stable patients, IL-2R, CH_{50} and anti-DNA antibody levels remained constant.

During the period of study 10 patients had a LN flare. This includes patients who initially lacked

Table 3 Serologic changes in LN remission

	Active n = 11	Remission n = 11	P <
IL-2R (u/ml)	1150 ± 160	678 ± 99	0.02
CH_{50} (u/ml)	105 ± 19	163 ± 19	0.04
Anti-DNA (iu/ml)	1108 ± 216	357 ± 93	0.005

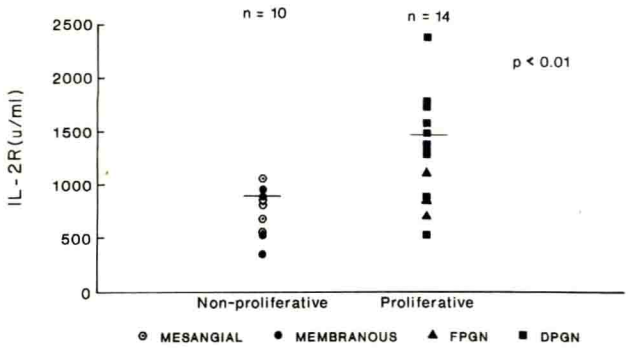

Fig. 3 Comparison of IL-2R levels in patients with proliferative versus non-proliferative histologic changes on renal biopsy

clinical evidence of nephritis as well as those patients with nephritis whose disease became more active. Figure 2 shows that mean IL-2R levels rose significantly with the disease flare. Initial IL-2R levels cover a wide range, from 300–1500 u/ml. Nine out of the 10 patients had further elevation of IL-2R with nephritis flare. Only 6 patients had either a fall in CH_{50} or a rise in anti-DNA levels with the nephritis flare and these changes were not statistically significant. Five of the 10 patients with nephritis flare had concurrent fever, rash, or arthralgias.

The presence or absence of proteinuria clearly had an effect on IL-2R level as those with proteinuria had higher levels than those without. However, linear regression correlations of IL-2R versus proteinuria were poor. Nephrotic range proteinuria was not associated with higher IL-2R levels.

During the study period 11 patients met criteria for remission of LN. Table 3 shows that these remissions were accompanied by a decrease in IL-2R, a rise in CH_{50} and a fall in anti-DNA antibody levels. Fifteen patients were seen initially but were unavailable for further follow-up.

Twenty-four patients with LN underwent renal biopsy. Those with evidence of proliferative nephritis were grouped together and compared to patients without evidence of cellular proliferation. As shown in Figure 3, mean IL-2R levels were significantly higher in the group of patients with diffuse or focal proliferative glomerulonephritis than in the group of patients with membranous nephropathy or mesangial changes. Although there was considerable overlap between the two groups at IL-2R levels <1000 u/ml, at higher levels, > 1400 u/ml, only proliferative glomerulonephritis was evident. Patients with diffuse proliferative glomerulonephritis (n = 11) had mean levels of 1465 ± 139 while those with focal proliferative glomerulonephritis (n = 3) had mean levels of 896 ± 98.

We also correlated interleukin-2 receptor levels with the histologic activity index. This correlation was statistically significant ($r = 0.66$, $p < 0.0005$). Weaker correlations were seen between CH_{50} and anti-DNA antibody levels versus activity index ($r = 0.6$, $p < 0.002$; $r = 0.48$, $p < 0.02$, respectively). There was also a significant correlation between the histologic chronicity index and IL-2R level, $r = 0.66$, $p < 0.0005$. However there was no correlation between chronicity index and CH_{50} or anti-DNA antibodies. There was a significant correlation between IgG and C3 deposition by immunofluorescence and IL-2R ($r = 0.51$, $p < 0.04$) but not with CH_{50} or anti-DNA levels. The correlation between the activity and chronicity indices was significant ($r = 0.61$, $p < 0.001$), suggesting that both types of histologic change may be due to a common factor.

To determine whether or not elevation in serum IL-2R level was simply due to decreased renal function, IL-2R levels and serum creatinine were measured in 187 sera from the 62 lupus patients. The range of serum creatinine for the entire group was 44 to 387 SI (0.5 to 4.4 mg/dl). There was no correlation between IL-2R and serum creatinine measured simultaneously ($r = 0.12$, $p = 0.54$). Nineteen other patients with non-immunologic forms of chronic renal disease with creatinine ranging from 106 to 466 SI (1.2 to 5.3 mg/dl) were also tested. This group included 8 with hypertensive nephrosclerosis, 4 with benign obstructive uropathy, 2 with renovascular disease, 3 with analgesics abuse, and 2 with non-specific chronic interstitial nephritis. Again, there was no correlation between serum IL-2R and creatinine ($r = 0.01$, $p = 0.97$).

Discussion

The results of this study show that soluble serum IL-2R levels correlate well with both clinical and histologic evidence of active proliferative lupus nephritis. Our preliminary data also suggest that a rise in IL-2R level during nephritis flare may be a more reliable serologic marker of activity than either anti-DNA antibody or CH_{50} levels. This is the first report of IL-2R measurements specifically correlated with lupus nephritis activity. Previous studies have reported IL-2R levels in relation to global SLE indices

[Campen et al. 1988, Semenzato et al. 1988, Wolf and Brelsford 1988, Tokano et al. 1989, Ter Borg et al. 1990]. Several groups have reported good correlation of IL-2R with lupus activity index [Campen et al. 1988, Tokano et al. 1989] while others could not confirm this [Ter Borg et al. 1990].

Elevated serum IL-2R levels have been found in patients with various forms of renal disease including idiopathic glomerulonephritis [Yorioka et al. 1990], nephrotic syndrome [Yorioka et al. 1990], renal transplantation [Waldmann 1990, Senitzer et al. 1991], and end-stage kidney disease [Beaurain et al. 1989]. Both immune system activation and decreased renal clearance have been suggested to account for elevated IL-2R levels in patients with glomerulonephritis or acute transplant rejection [Waldmann 1990, Yorioka et al. 1990]. Uremia may induce a state of T-cell activation [Beaurain et al. 1989]. One study of patients with glomerulonephritis reported a correlation between IL-2R and creatinine clearance [Yorioka et al. 1990]. However, our data did not confirm a strong correlation between IL-2R and serum creatinine, suggesting that immune activation, rather than decreased clearance, is a more likely reason for elevated IL-2R in LN. The strong correlation of chronicity index to IL-2R in our study may reflect the long-term chronic inflammatory state seen in these patients.

The biological role of soluble IL-2R is presently unknown but it may play an important role in the homeostatic control of the immune response. Excess circulating soluble IL-2R, by neutralizing interleukin-2 (IL-2R), might interfere with the availability of IL-2R to react with T-cells and consequently may be responsible for impairment of T-cell functions [Cantrell 1984].

To date there have been few studies of IL-2R levels and the clinical course in SLE. Patients with SLE generally have significantly higher IL-2R levels than normal controls [Campen et al. 1988, Semenzato et al. 1988, Wolf and Brelsford 1988, Tokano et al. 1989, Ter Borg et al. 1990], although the present study and another report [Schur 1987] show that patients with clinically inactive disease may have IL-2R levels similar to controls. Most of the available data related IL-2R level at one point in time to SLE activity, as defined by the number of organ systems involved [Campen et al. 1988, Semenzato et al. 1988], or C3 levels [Wolf and Brelsford 1988] or semiquantitative numerical disease activity index [Tokano et al. 1989]. While these studies suggest a positive correlation between IL-2R level and global disease activity, other investigators found no significant correlation between IL-2R and a lupus activity index at the time of disease exacerbation with patients studied prospectively [Ter Borg et al. 1990]. In addition, no correlation was noted between IL-2R levels and any specific organ system manifestation at the time of maximal disease activity [Ter Borg et al. 1990].

Four published studies have evaluated IL-2R levels in relation to other serologic tests in SLE. Decreased levels of C3 and C4 [Campen et al. 1988, Wolf and Brelsford 1988] and elevated cryoglobulins [Campen et al. 1988], correlated with elevated IL-2R levels. Anti-DNA antibodies were not assessed. In a more extensive prospective study, during disease exacerbations IL-2R levels correlated with C3, C4 and anti-DNA antibodies [Ter Borg et al. 1990]. With disease flare, IL-2R levels were higher in patients with depressed C3 or C4 levels compared to patients with normal complement levels. Within 6 months prior to disease exacerbation and at the time of exacerbation a similar percentage of patients showed elevations in IL-2R, anti-DNA antibodies and complement components. Five out of seven patients who had a disease flare without rises in anti-DNA antibodies had significant elevations in IL-2R levels. However, IL-2R levels did not give superior "advance warning" of disease exacerbation. In fact, the point at which significant change in levels was observed prior to exacerbation occurred later for IL-2R, at 3.5 weeks, than for anti-DNA, C3 or C4 which began to rise 9 weeks prior to exacerbation [Ter Borg et al. 1990]. A more limited study failed to show correlation between IL-2R, CH_{50} and anti-DNA antibody levels [Tokano et al. 1989]. The reasons for the conflicting results of these four studies are not clear but may be due to different patient selection and disease activity criteria.

There is surprisingly little information describing IL-2R levels during periods of stable disease activity. In fact only one patient has been previously reported with serial IL-2R levels during a period of stable activity in whom the levels did not change significantly [Ter Borg et al. 1990]. Our data in 26 patients with stable activity confirm this initial observation. In the setting of LN, the IL-2R level may be a reasonably specific indicator of disease activity if acute infection, which causes the level to rise [Rubin and Nelson 1990], can be excluded.

The role of IL-2R levels in the management of patients with SLE or LN is not yet defined. Certainly, IL-2R levels are not specific for LN. Our findings indicate that IL-2R is elevated when there is histologic evidence of focal or diffuse proliferative LN. This may prove to be clinically useful. Additional studies are needed to determine whether or not IL-2R may serve as an early marker of impending disease flare in LN or whether IL-2R levels over a period of time have prognostic value as they may have in various neoplastic disease [Waldmann 1990]. Studies are also needed to determine whether IL-2R levels may be particularly useful in LN patients with persistent low complement

levels but without obvious disease activity or in SLE patients with normal anti-DNA antibody levels during disease flares.

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Detection and clinical usefulness of urinary interleukin-6 in the diseases of the kidney and the urinary tract

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Abstract. Interleukin-6 (IL-6) plays a key role in inflammatory and immune responses in the host. In the present study, the IL-6 activity in urine from patients with various renal diseases was examined to elucidate the pathological and clinical significance of urinary IL-6. In patients with mesangial proliferative glomerulonephritis (mes-PGN) including, IgA nephropathy, the urinary IL-6 activity tended to increase with the progression of mesangial hypercellularity. In four patients with IgA nephropathy, urinary IL-6 activity increased markedly but transiently during episodes of acute exacerbation associated with upper respiratory tract infection. In addition, it was demonstrated that urine from patients with other types of PGN such as poststreptococcal acute glomerulonephritis and membranoproliferative glomerulonephritis contained large quantities of IL-6. However, the levels of urinary IL-6 activity were almost within the normal range in non-proliferative glomerular diseases such as membranous nephropathy, minimal change nephrotic syndrome and lupus nephritis (WHO class I and V), non-glomerular bleeding and orthostatic proteinuria. It should be noted that a marked increase in urinary IL-6 was often observed in the patients with urinary tract infection. These results indicated that IL-6 in urine might be derived from various types of cells participating in inflammatory reactions not only in the renal parenchyma but also in the urinary tract.

Key words: interleukin-6 (IL-6) – renal disease – disease of the urinary tract

Introduction

Interleukin-6 (IL-6) is one of cytokines involved in inflammatory responses as well as in immune reactions in the host [Hirano and Kishimoto 1990]. It has been shown that IL-6 has a vast spectrum of biological activities and acts on various cell types in vivo as well as in vitro. IL-6 can be produced by a variety of cell types, including monocytes, T cells, B cells, keratinocytes, vascular endothelial cells and fibroblasts [Hirano and Kishimoto 1990]. In addition to its physiological role, IL-6 has been proposed to be associated with the pathogenesis of certain disease conditions, including multiple myeloma, cardiac myxoma, and rheumatoid arthritis [Kawano et al. 1988, Kishimoto and Hirano 1988, Hirano et al. 1988]. Horii et al. [1989] have recently demonstrated that IL-6 could be produced by mesangial cells and might be involved in mesangial proliferative glomerulonephritis (mes-PGN). Increased urinary IL-6 has been described in renal transplant recipients [Van Oers et al. 1988]. However, whether urinary IL-6 might originate exclusively from mesangial cells or from other types of cells as well is not known. The present study was undertaken to examine the IL-6 activity in various renal diseases to assess the clinical usefulness of urinary IL-6.

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Materials and methods

Subjects

A total of 82 patients (32 males and 50 females) were enrolled in the present study. Mean age of the patients was 34 years (4 months – 72 years). Duration of these diseases was various (several days – several decades). Included among these were, 43 cases of mesangial proliferative glomerulonephritis (mes-