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Multicenter clinical trial of recombinant human insulin-like growth factor I in patients with acute renal failure

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Background. Patients with acute renal failure (ARF) have high morbidity and mortality rates, particularly if they have serious comorbid conditions. Several studies indicate that in rats with ARF caused by ischemia or certain nephrotoxins, insulin-like growth factor-I (IGF-I) enhances the recovery of renal function and suppresses protein catabolism.

Methods. Our objective was to determine whether injections of recombinant human IGF-I (rhIGF-I) would enhance the recovery of renal function and is safe in patients with ARF. The study was designed as a randomized, double-blind, placebo-controlled trial in intensive care units in 20 teaching hospitals. Seventy-two patients with ARF were randomized to receive rhIGF-I (35 patients) or placebo (37 patients). The most common causes of ARF in the rhIGF-I and placebo groups were, respectively, sepsis (37 and 35% of patients) and hypotension or hemodynamic shock (42 and 27% of patients). At baseline, the mean (± SD) APACHE II scores in the rhIGF-I and placebo-treated groups were 24 ± 5 and 25 ± 8, respectively. In the rhIGF-I and placebo groups, the mean (median) urine volume and urinary iothalamate clearances (glomerular filtration rate) were 1116 ± 1037 (887) and 1402 ± 1183 (1430) ml/24 hr and 6.4 ± 5.9 (4.3) and 8.7 ± 7.2 (4.4) ml/min and did not differ between the two groups. Patients were injected subcutaneously every 12 hours with rhIGF-I, 100 μg/kg desirable body weight, or placebo for up to 14 days. Injections were started within six days of the onset of ARF. The primary endpoint was a change in glomerular filtration rate from baseline. Other end points included changes from baseline in urine volume, creatinine clearance and serum urea, creatinine, albumin and transferrin, frequency of hemodialysis or ultrafiltration, and mortality rate.

Results. During the treatment period, which averaged 10.7 ± 4.1 and 10.6 ± 4.5 days in the rhIGF-I and placebo groups, there were no differences in the changes from baseline values of the glomerular filtration rate, creatinine clearance, daily urine volume, or serum urea nitrogen, creatinine, albumin or transferrin. In patients who did not receive renal replacement therapy, there was also no significant difference in serum creatinine and urea between the two groups. Twenty patients in the rhIGF-I group and 17 placebo-treated patients underwent dialysis or ultrafiltration. Twelve rhIGF-I–treated patients and 12 placebo-treated patients died during the 28 days after the onset of treatment.

Conclusions. rhIGF-I does not accelerate the recovery of renal function in ARF patients with substantial comorbidity.

Key words: ischemia, nephrotoxicity, protein catabolism, comorbidity in ARF, hemodynamics.

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Acute renal failure (ARF) is a common event in hospitalized patients, particularly in those requiring intensive care [1]. It is associated with an increased risk for morbidity and mortality. The mortality rate in patients with ARF tends to be strongly influenced by their underlying comorbid conditions. The mortality rate in ARF patients with comorbid conditions has been estimated to be as high as 80 to 85% in some series [1–4]. ARF also complicates the medical management of hospitalized patients

and may itself contribute to morbidity and mortality. Hence, a treatment that would accelerate the recovery of renal function in patients with ARF might be expected to reduce morbidity and possibly mortality, and could reduce the cost of medical care.

Recombinant human insulin-like growth factor I (rhIGF-I) is a 70-amino acid polypeptide growth factor with structural homology to insulin. IGF-I is an anabolic agent that mediates many actions of growth hormone and mimics some actions of insulin. In addition to its many metabolic effects, rhIGF-I increases renal blood flow and glomerular filtration rate (GFR) in rats, normal adult humans, and patients with chronic renal failure [5–11]. rhIGF-I also accelerates the recovery of renal function, enhances the healing of the injured nephron, and reduces mortality in animals with ischemic, toxic, or endotoxin-induced experimental ARF [10, 12–17]. These beneficial effects on the kidney appear to be due to the vasoactive, mitogenic, and other metabolic effects of rhIGF-I [13, 18].

In the doses currently used, rhIGF-I has been administered by subcutaneous injections to normal subjects and patients with chronic renal failure with few side effects. Because of its beneficial effects in rats with ARF and apparent safety in humans, we examined whether rhIGF-I will accelerate recovery from ARF in patients. A multicenter, double-blind, randomized, placebo-controlled clinical trial was performed. Two hypotheses were tested: (*a*) that rhIGF-I will increase the rate of recovery of renal function in patients with ARF, and (*b*) that rhIGF-I can be administered safely to these individuals.

METHODS

Study protocol

Twenty clinical centers participated in this trial. Patients with ARF were randomized to receive, in a double-blinded fashion, subcutaneous injections of either rhIGF-I, 100 μg/kg desirable body wt, or equal volumes of placebo every 12 hours at 9:00 a.m. and 9:00 p.m. The injections were continued for 14 consecutive days. The appearances of the rhIGF-I and placebo were indistinguishable. The bioactivity of each rhIGF-I batch that was used in this study had been tested in a standardized assay measuring the mitogenic response of quiescent MG-63 cells, a human osteosarcoma cell line. Desirable body weight was determined from the Metropolitan Life Insurance Tables [19]. This report describes the results in 72 patients with ARF.

Patients were accepted into the study if they satisfied the following criteria: age, 18 to 80 years; a diagnosis of ARF, as defined by a rise in serum creatinine from a baseline value of less than 1.8 to 3.0 mg/dl or greater or an acute decrease in creatinine clearance to 25 ml/min or less following surgery, trauma, hypotension, or sepsis; persistence of ARF after intravenous infusion of sufficient fluids, if clinically indicated; a fractional excretion of sodium of 1.0% or greater in oliguric patients (urine less than 500 ml/24 hr); and a commitment by the patient and medical staff for renal replacement therapy and aggressive life-supporting measures, if medically indicated.

Exclusion criteria included the following: the onset of ARF more than six days before commencement of the screening studies (discussed later in this article); irreversible disease expected to result in a rapidly fatal outcome; an acute physiology and chronic health evaluation (APACHE II) score [20, 21] of greater than 37 during the 24-hour period preceding screening; renal failure caused by obstruction of the urinary tract, x-ray contrast nephropathy, or bilateral renal vascular obstruction. Other exclusion criteria were: chronic renal failure, the hepatorenal syndrome, interstitial nephritis, or glomerulonephritis; renal allograft; solitary kidney; persisting hypotension (systolic blood pressure less than 90 mm Hg) after fluid resuscitation and in the absence of afterload reduction or antihypertensive therapy; vasopressor treatment within 12 hours of study entry (except for dopamine at less than 10 μg/kg/min); known or suspected cancer (except basal cell carcinoma) within the preceding two years; known hypersensitivity to human insulin, rhIGF-I, iodine or shellfish; and pregnancy, HIV infection, or treatment with another investigational agent within the preceding 28 days. This study was approved by the institutional review board for human research at each participating center, and informed written consent was obtained from each study participant or his/her family members.

Upon entering the study, each patient underwent a 24-hour baseline screening period. During this period, a detailed medical history was obtained. A physical examination was performed. The APACHE II score was calculated, and a chest x-ray, echocardiogram, complete blood count, serum chemistry panel, urinalysis, and measurement of urine sodium, potassium, and creatinine were obtained. The creatinine clearance and the GFR (iothalamate clearance) were measured using fractional urine collections over a three-hour period.

Patients began treatment with rhIGF-I or placebo after baseline measurements were completed. On each day of the study, vital signs, 24-hour urine volume, and body weight were recorded. Complete blood counts and routine serum chemistries were obtained on each day of study. Blood glucose was measured before and two hours after each injection. At baseline and on days 4, 9, and 13 of the study, the clearances of iothalamate and creatinine were measured as described later in this article. Serum IGF-I was measured at baseline and on days 4, 9, and 13 at approximately 12 hours after the most recent administration of rhIGF-I or placebo. Serum IGF-binding

protein (IGFBP)-2 and IGFBP-3 levels were measured at baseline and on days 1, 4, 8, 12, and 14.

Throughout the study, patients were provided with standard clinical care by their usual medical personnel. Blood products and nonstudy medications were administered, and laboratory tests were obtained as medically indicated. Patients were given adequate nutritional support by either the enteral or parenteral route with an attempt to provide energy intakes of 2000 to 2500 kcal/day and 1.0 to 1.5 g/kg of protein. The decision to begin renal replacement therapy (hemodialysis or continuous venovenous hemodiafiltration) was made by individual study physicians using the following rules as determined in the study protocol: acidemia (serum bicarbonate concentration of less than 12 mM), hyperkalemia (serum potassium of more than 6.5 mM), rapid rise in serum urea nitrogen (SUN; of more than 45 mg/dl per day), severe azotemia (SUN of more than 120 mg/dl), hypernatremia or hyponatremia ($160 < Na^+ < 120$ mM), fluid overload or pulmonary edema (clinical examination or chest x-ray), uremic pericarditis, or central nervous system abnormalities (clinical examination).

Measurement of glomerular filtration rate

Iothalamate clearances were considered to indicate the GFR. Iothalamate clearances were measured in the mornings on the days indicated earlier in this article, and the administration of rhIGF-I or placebo was delayed until the clearance measurement was completed. A serum and urine sample were obtained. Nonradioactive iothalamate, 1500 mg (5 ml of Conray® 30; Mallinckrodt, St. Louis, MO, USA), was injected intravenously as a bolus. A timed urine specimen was collected from an indwelling bladder catheter or by bladder voiding for the first 60 minutes after the iothalamate injection. This one-hour urine collection was used for the measurement of urinary creatinine and calculation of the creatinine clearance. This period of 60 minutes also allowed for distribution of exogenously administered iothalamate into the extracellular space. Subsequently, four consecutive 30-minute urine collections were obtained, and a serum sample was drawn at the beginning and end of each of these collection periods. Each of these latter samples was then used for the measurement of iothalamate and calculation of the iothalamate clearance. Although renal failure is one of the risk factors for contrast medium-induced acute nephropathy when large amounts of radiation contrast media are given, the very small dose of iothalamate used as a GFR marker in this and other studies has not been associated with renal injury and is believed to be safe.

Laboratory methods

Except as indicated later, the blood counts and serum and urine chemistries were measured in the hospital clinical laboratory of each participating center using routine clinical laboratory methods. Serum samples for the IGF-I assay were frozen at −20°C and measured in a central laboratory. Serum was chromatographed on a 0.9×100 cm column containing Sephadex F-50 (fine), using 0.25 M formic acid to separate IGF-I from its serum-binding proteins as previously described [22]. Serum IGF-I was measured by a specific radioimmunoassay that used an antiserum kindly provided by Drs. L.E. Underwood and J.J. Van Wyk (Chapel Hill, NC, USA) and distributed for research use through the National Hormone and Pituitary Program. Serum anti-IGF-I antibodies were measured in the rhIGF-I–treated patients using an enzyme-linked immunosorbent assay (ELISA) as previously described [23]. Serum IGFBP-2 levels were measured by ELISA as previously described [24, 25], and IGFBP-3 was measured by ELISA using a commercially available kit (Diagnostic Systems Laboratory, Webster, TX, USA). Both assays were performed in a central laboratory. Iothalamate levels in serum and urine were measured in a central laboratory using previously described methods [26]. All personnel who handled the specimens or performed the chemical measurements were blinded as to what treatment an individual patient was given.

Statistical methods

All data are presented as mean ± 1 SD unless stated otherwise. Differences between treatment groups and changes from baseline for each laboratory parameter were tested using analyses of variance (ANOVA) methods. Significance of differences was assumed at a P of less than 0.05. Although the protocol specified that at entry creatinine clearance should be no greater than 25 ml/min, there were nine patients with values outside of this range at baseline. Data from these patients were excluded from the efficacy analysis.

RESULTS

Thirty-five patients were randomized to receive rhIGF-I treatment, and 37 subjects were randomized to the placebo. Characteristics of these patients are shown in Table 1. There were no differences between the two groups with regard to age, gender or racial distribution, body weight, APACHE II scores, or prevalence of oligoanuria at baseline. However, the number of patients with hypotension or hemodynamic shock as the cause for ARF was significantly greater in the rhIGF-I group (42%) compared with the placebo group (27%, $P < 0.05$). All patients were hospitalized in intensive care units at the onset of the study. The primary causes of ARF are shown in Table 2. Sepsis and hypotension or hemodynamic shock were the most commonly listed causes for ARF in both groups of patients. Surgery was

Table 1. Characteristics of patients with acute renal failure

	rhIGF-I	Placebo
Number of subjects	35	37
Age *years*	56.4 ± 17.2	55.8 ± 19.0
Gender, male:female %	46:54	59:41
Racial distribution %		
Caucasian	57	73
African American	20	22
Other	23	5
Weight *kg*	86.2 ± 21.9	84.2 ± 27.3
Desirable body weight *kg*	62.1 ± 7.9	63.7 ± 9.2
APACHE II score	24.4 ± 5.0	25.0 ± 7.5
Number of patients with baseline urine volume		
< 500 ml/24 hours	12	11
≥ 500 ml/24 hours	23	26

Data are mean ± standard deviation.

Table 2. Primary cause of acute renal failure

Primary cause of ARF	rhIGF-1	Placebo
Sepsis	37%	35%
Hypotension	42%	27%
Surgery	11%	16%
Aminoglycosides	3%	5%
Other/unknown	6%	16%

the third most common primary cause for ARF in each group.

The mean and median number of injections of rhIGF-I or placebo in individual patients averaged 20.3 ± 8.7 (median, 24) injections in the rhIGF-I group and 19.6 ± 9.1 (median, 21) in the placebo group. The mean number of injections was similar in the rhIGF-I and placebo groups and was less than the maximum total number of injections that were possible per patient, which was 28. Reasons for the reduced number of injections included the death of subjects prior to finishing the 14 days of treatment (discussed later in this article); the mean duration of treatment with rhIGF-I and placebo was 10.7 ± 4.1 and 10.6 ± 4.5 consecutive days, respectively. During the treatment period, blood glucose concentrations below 60 mg/dl were observed on two occasions, one each in the rhIGF-I–treated and the placebo-treated groups. Subjects treated with rhIGF-I received a cumulative dose of 128 ± 59 mg (median value, 137 mg) of this hormone during their entire study. There were no clinically important side-effects that were attributable to rhIGF-I.

Serum IGF-I concentrations at baseline in most subjects were below normal values (Table 3). Serum IGF-I levels at baseline were 124 ± 67 and 102 ± 53 ng/ml in the rhIGF-I and placebo-treated groups, respectively (P = NS). During the treatment period, serum IGF-I concentrations rose approximately four to five times in only the rhIGF-I patients and were unchanged in the placebo-treated individuals (Table 3).

Renal function

At baseline, urine flow rates were 1116 ± 1037 and 1402 ± 1183 ml/24 hr in the rhIGF-I and placebo-treated groups, respectively. During each day of the treatment period, urine volumes were not significantly different between either the entire group of rhIGF-I–treated patients versus placebo patients or between those patients in the rhIGF-I (N = 23) versus the placebo (N = 26) groups who were not oliguric at baseline (Fig. 1). Twelve of 35 rhIGF-I patients and 11 out of 37 patients in the placebo group were oliguric or anuric at baseline (that is, a daily urine volume less than 500 ml). Among the oligoanuric rhIGF-I– and placebo-treated patients, urine volumes at baseline were 163 ± 131 and 245 ± 156 ml/24 hr, respectively. In both subgroups, daily urine flow rates increased significantly during the 14 days of study. This increase in urine volume above baseline values tended to be greater in the placebo group as compared with the rhIGF-I–treated oliguric subjects, although this trend was not statistically significant (P = 0.246).

Fifty evaluable subjects underwent iothalamate clearance measurements at baseline. This measurement was not performed in the remaining 22 patients because of insufficient urine flow rates to conduct the clearance measurement. The iothalamate clearances at baseline were 6.4 ± 5.9 (median, 4.3) ml/min (N = 23) in the subjects receiving rhIGF-I and 8.7 ± 7.2 (median, 6.3) ml/min (N = 27) in the placebo group (Fig. 2A). As expected, baseline iothalamate clearances were slightly greater in the rhIGF-I– and placebo-treated nonoliguric patients than in those who were oliguric. In the rhIGF-I– and placebo-treated patients who during baseline were oliguric, their median baseline iothalamate clearances were 0.5 ml/min (N = 7) and 5.0 ml/min (N = 8), respectively (Fig. 2B). In the oligoanuric as well as nonoliguric patients in both the rhIGF-I and placebo groups, the iothalamate clearances tended to increase over the 14-day period of study (Fig. 2). There was no difference in the rate of increase in iothalamate clearances from baseline or in the absolute values of these clearances at any time point between the rhIGF-I versus the placebo groups; this was also observed when the nonoliguric or oligoanuric patients were analyzed separately as well as for the nonoliguric and oligoanuric patients combined (Fig. 2). Thus, treatment with rhIGF-I, as compared with placebo, did not appear to accelerate the recovery of GFR in patients with ARF.

The foregoing findings are also supported by the creatinine clearances in both study groups (Fig. 3). The creatinine clearances were not different between the rhIGF-I and placebo groups at baseline or at any time during the treatment phase. When the creatinine clearances were analyzed according to the daily urine flow, again there

Table 3. Serum chemistries in patients with acute renal failure treated with rhIGF-I or placebo

	Day of study							
	Baseline	3	5	7	8	10	12	14
No. of patients in study								
rhIGF-I	35	34	31	29	27	25	20	18
Placebo	37	34	32	29	27	25	20	18
Serum urea nitrogen *mg/dl*[a]								
Normal range: 10–20								
rhIGF-I	62.6 ± 29.3	79.5 ± 38.0	79.7 ± 36.6	84.2 ± 41.4	76.6 ± 36.9	75.3 ± 41.0	75.7 ± 39.5	93.2 ± 75.6
Placebo	76.0 ± 32.1	81.3 ± 33.3	86.1 ± 35.8	84.2 ± 32.0	88.6 ± 30.0	77.3 ± 20.7	76.9 ± 21.5	73.1 ± 30.4
Serum creatinine *mg/dl*[a]								
Normal range: 0.5–1.2								
rhIGF-I	6.2 ± 6.7	4.7 ± 2.3	4.3 ± 2.4	4.2 ± 2.8	5.3 ± 6.7	3.8 ± 2.5	3.7 ± 2.5	4.0 ± 2.4
Placebo	7.7 ± 11.8	7.0 ± 12.7	4.3 ± 2.1	3.8 ± 1.8	4.0 ± 1.8	3.6 ± 1.7	3.2 ± 1.6	2.8 ± 1.4
Serum albumin *g/dl*								
Normal range: 3.5–5.0								
rhIGF-I	2.33 ± 0.82	2.16 ± 0.67	2.35 ± 0.81	2.24 ± 0.76	—	2.34 ± 0.78	2.36 ± 0.56	2.19 ± 0.65
Placebo	2.56 ± 0.66	2.35 ± 0.50	2.40 ± 0.56	2.32 ± 0.53	—	2.22 ± 0.62	2.24 ± 0.59	2.31 ± 0.59
Serum transferrin *mg/dl*								
Normal range: 252–429								
rhIGF-I	112 ± 47	117 ± 49	112 ± 43[b]	100 ± 33	—	110 ± 41[c]	108 ± 60	92 ± 38[b]
Placebo	120 ± 55	123 ± 55	130 ± 50	130 ± 52	—	148 ± 67	130 ± 73	149 ± 52

	Day of Study			
	Baseline	4	9	13
Serum IGF-I *ng/dl*				
Normal range: 170–230				
rhIGF-I	124 ± 76	535 ± 213[c]	576 ± 280[c]	603 ± 230[c]
Placebo	102 ± 53	136 ± 89	133 ± 69	146 ± 77

Data are mean ± standard deviation.
[a] Excludes patients who underwent renal replacement therapy
[b] $P \leq 0.05$
[c] $P = 0.01$ rhIGF-I vs. placebo

were no differences among the oligoanuric or nonoliguric patients between the two treatment groups (Fig. 3B). The oliguric subjects who were randomized to receive rhIGF-I tended to have lower creatinine clearances at each time point, although the changes from baseline levels in the rhIGF-I patients were not significantly different from the placebo groups.

At baseline in the patients who had not received hemodialysis or continuous ultrafiltration, serum creatinine concentrations were 6.2 ± 6.7 and 7.7 ± 11.8 mg/dl in the rhIGF-I and placebo groups, respectively. In both groups, serum creatinine levels decreased substantially over the 14-day period of study (Table 3). At each time point, there were no differences in the serum creatinine levels between the rhIGF-I– and placebo-treated patients who did not receive dialysis or ultrafiltration (Table 3).

Metabolic data

At baseline in the patients who did not receive renal replacement therapy, SUN levels were similar in the rhIGF-I– (63 ± 29 mg/dl) and placebo-treated (76 ± 32 mg/dl) patients. The change from baseline in SUN was not different in either the nonoliguric or total group of rhIGF-I– versus placebo-treated patients on any day of the study (Table 3). In the oliguric patients, SUN increased significantly more from baseline in the rhIGF-I group relative to the placebo-treated patients on days 10 and 11 ($P < 0.05$). The SUN did not decrease significantly below baseline values during the two weeks of study, even though the serum creatinine levels fell during this period of time.

At baseline, serum albumin levels were reduced below normal in both the rhIGF-I and placebo-treated groups and were 2.33 ± 0.82 and 2.56 ± 0.66 g/dl, respectively (Table 3). During the treatment period, serum albumin tended to be lower in the rhIGF-I group as compared with placebo, although the differences were not significant. Serum albumin concentrations did not change during the course of study in either group (Table 3).

Serum transferrin concentrations were below normal at baseline and similar in the rhIGF-I– (112 ± 47 mg/dl) and placebo-treated groups (120 ± 55 mg/dl; Table 3). Serum transferrin levels tended to rise in the placebo group, although not significantly. On days 5, 10, and 14 of treatment, serum transferrin concentrations decreased significantly more in the rhIGF-I group as compared with placebo ($P < 0.05$; Table 3). Serum transferrin tended to be lower in the rhIGF-I versus the placebo-treated patients both in those with APACHE II scores of less

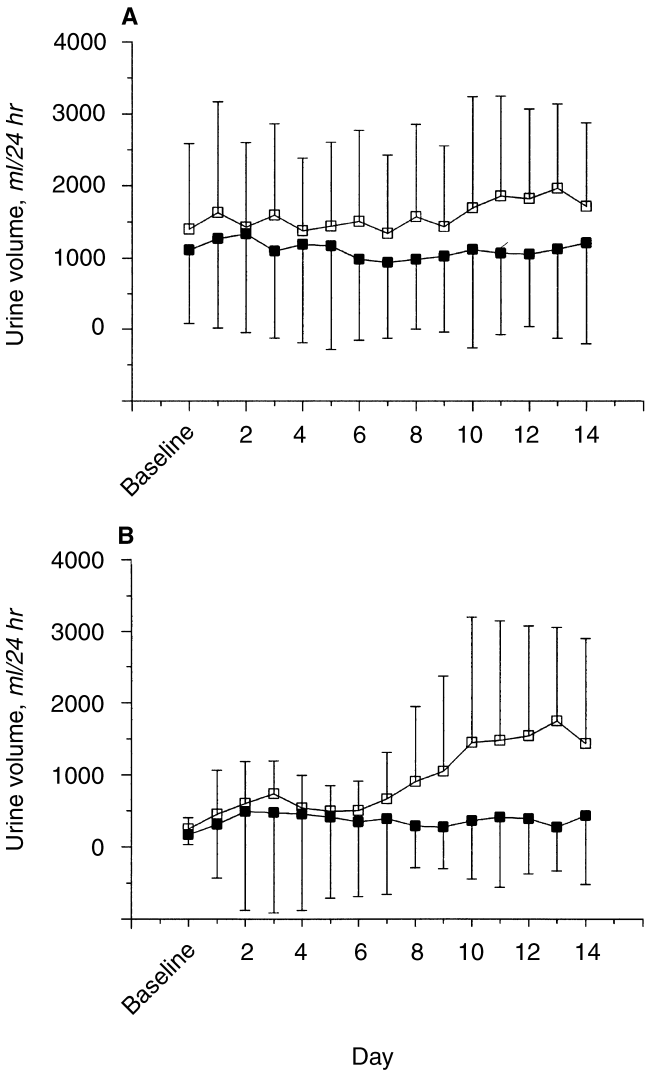

Fig. 1. (*A*) Daily urine excretion in study participants randomly assigned to recombinant human insulin-like growth factor I (rhIGF-I; ■; *N* = 35) or placebo (□; *N* = 37). Data are mean ± SD. Values are not significantly different. (*B*) Daily urine excretion in subjects who were oliguric or anuric at baseline (urine volume of less than 500 ml/24 hr) and treated with rhIGF-I (■; *N* = 12) or placebo (□; *N* = 11), respectively. Data are mean ± SD. Values are not significantly different.

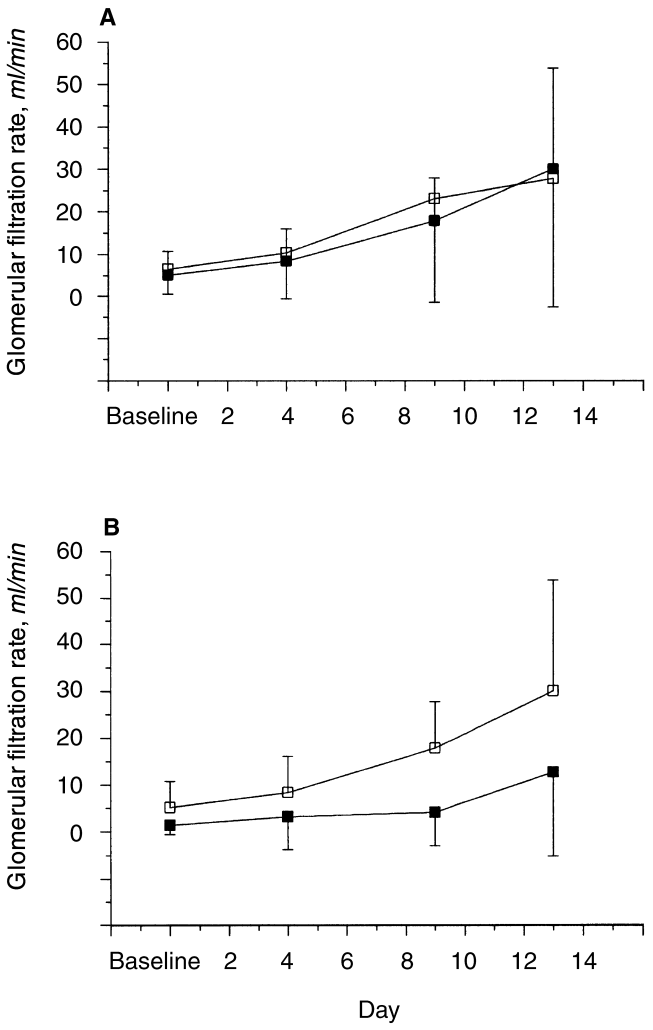

Fig. 2. (*A*) Glomerular filtration rate measured as clearance of iothalamate in all study participants with sufficient urine flow rates, receiving rhIGF-I (■; *N* = 22) or placebo (□; *N* = 27). Data are mean ± SD. Values are not significantly different. (*B*) Glomerular filtration rate in subjects who were oliguric at baseline and who had urine flow rates sufficient for the measurement of iothalamate clearance treated with rhIGF-I (■; *N* = 7) or placebo (□; *N* = 8), respectively. Data are mean ± SD. Values are not significantly different.

than 25 and in those with APACHE II scores of 25 or greater. Indeed, serum transferrin decreased significantly more in the rhIGF-I–treated patients with APACHE II scores of less than 25 on day 10 and in those with APACHE II scores of 25 or greater on day 14. There were no differences between the rhIGF-I– and placebo-treated groups with regard to the change in 24-hour urinary excretion of sodium, potassium, phosphorus, or protein (data not shown).

Serum IGFBP-2 levels tended to increase during the first four days of study in subjects receiving rhIGF-I (Fig. 4A), but the values were not statistically different from baseline nor from those measured in the placebo group at any time during the two weeks of study. At baseline, IGFBP-3 levels were very low compared with the normal reference range (3300 to 7260 ng/ml). At baseline, IGFBP-3 levels in the rhIGF-I group were 1804 ± 125 (SEM) ng/ml in the patients subsequently receiving rhIGF-I and 1842 ± 143 (SEM) ng/ml in the placebo subjects. Serum IGFBP-3 levels tended to decrease in the rhIGF-I group toward the end of the two-week study, but this trend was statistically not significant (Fig. 4B).

Incidence of renal replacement therapy and mortality rate

Twenty patients in the rhIGF-I group (57%) and 17 placebo-treated patients (46%) underwent renal replace-

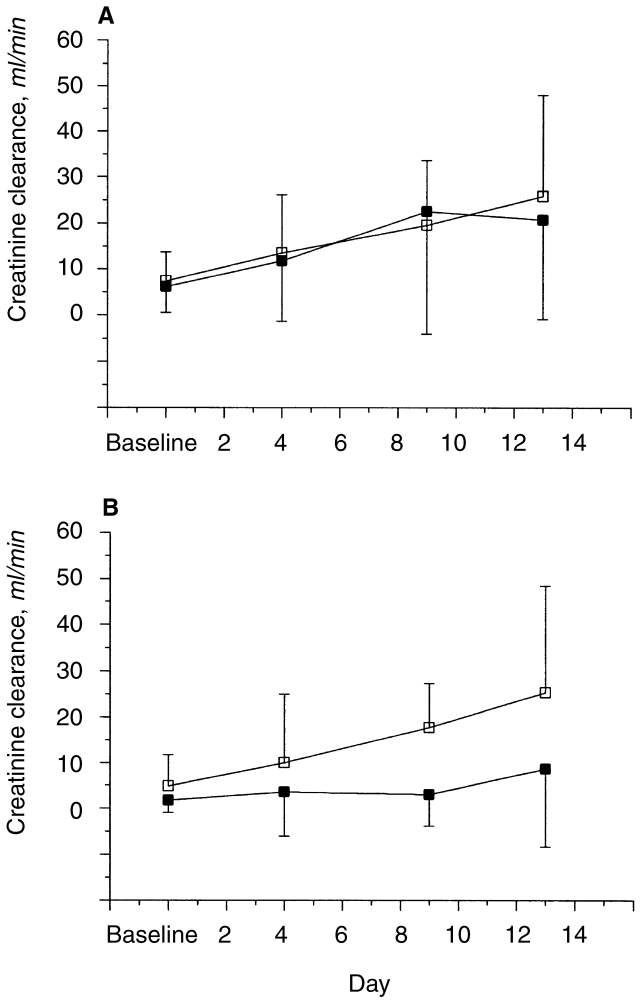

Fig. 3. (*A*) Creatinine clearances in all subjects with sufficient urine flow rates, receiving rhIGF-I (■) or placebo (□), respectively. Data are mean ± SD. Values are not significantly different. (*B*) Creatinine clearances in subjects who were oliguric at baseline receiving rhIGF-I (■) or placebo (□). Data are mean ± SD. Values are not significantly different.

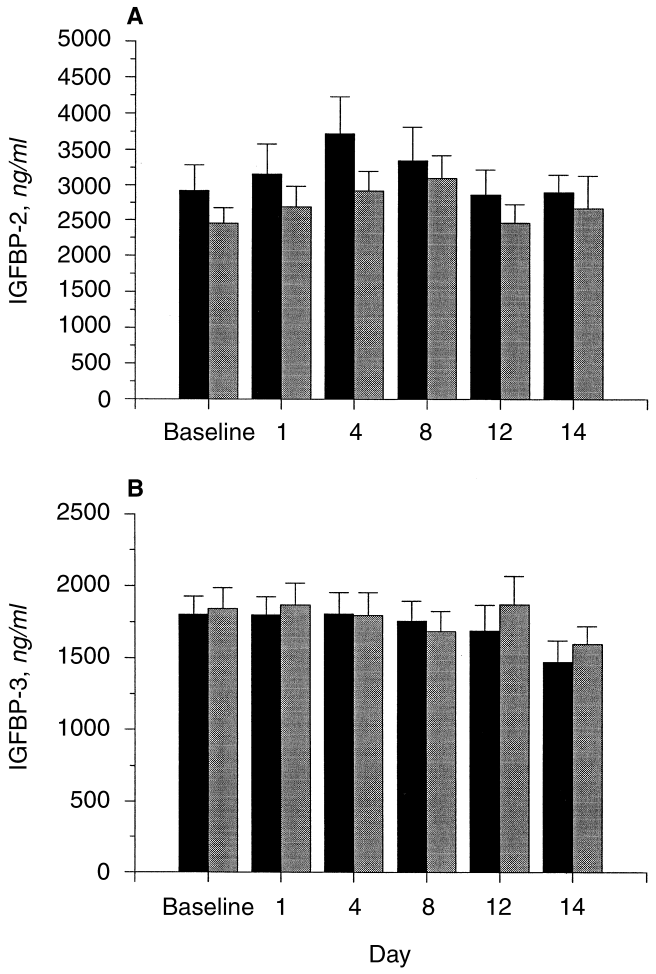

Fig. 4. Serum levels of IGF-binding protein-2 (*A*) and IGF-binding protein-3 (*B*) in subjects receiving rhIGF-I (■) or placebo (▒). Data are mean ± SEM.

ment therapy during the study (Table 4). Most of the dialyzed patients had been treated with renal replacement therapy at or before baseline, indicating that ARF was well established in these patients at the onset of this study. There was no difference in the number or type of renal replacement treatments provided to the two groups of patients. Ten rhIGF-I–treated patients (29%) and 11 placebo-treated patients (30%) died during the 14-day treatment phase of the study. The median numbers of days of survival during treatment of these 21 patients were seven and nine days, respectively. By day 28 after the onset of the treatment phase, 12 rhIGF-I– and 12 placebo-treated patients had died. In the rhIGF-I–treated group, five oligoanuric and seven nonoliguric patients died on or before day 28. In the placebo group, six oligoanuric and six nonoliguric patients died by this day. Overwhelming sepsis or cardiopulmonary failure was the most commonly reported cause of death in both groups.

DISCUSSION

In rats with experimental ARF, rhIGF-I can accelerate the rate of recovery of renal function. The increase in renal function may begin within hours of commencing rhIGF-I treatment [13], suggesting that at least part of the rise in renal function is due to hemodynamic factors, that is, an increase in renal blood flow and filtration fraction leading to an increase in GFR [7]. RhIGF-I also stimulates cell mitosis and can apparently promote healing of the structural nephron lesions associated with ischemic or some toxic injuries to the kidney. Moreover, rhIGF-I has anabolic effects. In rats with ARF, rhIGF-I reduces the urea nitrogen appearance (net urea generation) and stimulates protein synthesis and suppresses

Table 4. Renal replacement therapy

	rhIGF-I ($N = 35$)	Placebo ($N = 37$)
No. of patients receiving RRT during study	20	17
Days of RRT	9.2 ± 6.8	6.4 ± 6.0
RRT rate *treatments per day*	0.5 ± 0.3	0.5 ± 0.3
No. of patients who received RRT at or before baseline	14	9
Days on RRT in patients started on RRT at or before baseline	10.3 ± 7.0	7.8 ± 7.2

Data are mean ± standard deviation. Abbreviation is: RRT, renal replacement therapy (intermittent hemodialysis, continuous venovenous hemofiltration or hemodiafiltration).

protein degradation in skeletal muscle [13]. These findings provided a rationale for the use of rhIGF-I for the treatment of ARF in humans.

This clinical trial in patients with ARF does not indicate that rhIGF-I either improves the GFR or accelerates the rate of recovery of renal function. In fact, in surviving patients who were oliguric at baseline and received rhIGF-I, improvements in GFR and urine flow rate tended to occur more slowly compared with placebo-treated subjects (Figs. 1B, 2B, and 3B). Moreover, treatment with rhIGF-I did not suppress the rate of rise of the SUN or improve serum albumin or transferrin concentrations. Administration of rhIGF-I to these patients did not promote diuresis or affect the urinary excretion of sodium, potassium, phosphorus, or protein. Other adverse events were minor and similar in the two groups, and serum antibodies to IGF-I were not detected in either group.

The lack of an effect of rhIGF-I on GFR or rate of recovery of renal function could be due to several factors. First, it is possible that rhIGF-I does not act on human kidney as it does on rat kidney. Although this possibility cannot be excluded, published research does not support this contention. In both normal rats and humans, the administration of rhIGF-I increases renal blood flow and GFR [5–9, 27]. In addition, in normal rats and in humans with chronic renal failure, the administration of rhIGF-I is reported to increase renal size [11, 28]. Moreover, in both rats and humans with chronic renal failure, rhIGF-I stimulates anabolic processes [29, 30].

Another possible cause for the lack of effect of rhIGF-I is that the renal lesions of ARF in rats and humans are different. However, research suggests that both functional and anatomical manifestations of ischemia- or nephrotoxin-induced ARF are similar in rats and humans [31]. Indeed, experimental ARF in the rat is commonly used as a model to study the pathogenesis, pathophysiology, and anatomic pathology of ARF in humans.

On the other hand, there are certain distinct differences between humans with ARF and rats with experimental ARF. One such difference is that in rats, experimental ARF is created as an isolated disorder. Indeed, when ARF is created surgically, the control rats are usually sham operated and pair fasted so that the ARF can be investigated as an isolated event. In contrast, in humans, ARF is often superimposed on severe clinical illnesses, frequently in a setting of profound metabolic disturbances.

In the patients in this study, the high APACHE II scores and the causes of their ARF (Tables 1 and 2) indicate that they were very ill. The fact that all of the patients were hospitalized in intensive care units at the onset of the study and that their mean serum albumin and transferrin concentrations were very low provide further support that these patients had other severe illnesses and disturbed metabolism. It is possible that these comorbid conditions might cause reinjury of nephrons, prevent nephron healing, or abrogate the effects of rhIGF-I in these patients possibly by continued or recurrent sepsis, hemodynamic instability with episodes of renal hypoperfusion, increased release of cytokines or microbial toxins (for example, endotoxin), or the administration of nephrotoxic medicines.

The lack of bioactivity of the rhIGF-I batches does not account for the failure to achieve beneficial therapeutic results in this trial. First, each batch of recombinant peptide had been tested for bioactivity in a mitogenicity assay by the manufacturer. Second, in several experimental and clinical studies using the same compound obtained from the same manufacturer, rhIGF-I increased renal function and affected the metabolic parameter [5–9, 13, 30, 32–34].

Another possible explanation for the lack of effect of rhIGF-I is that the first dose of the hormone was administered as late as six days after the onset of ARF. This protocol design was used in order to allow time for the diagnosis of ARF, to obtain informed consent, and to perform baseline studies. In experimental rat models of ARF, rhIGF-I has been shown to enhance the recovery of renal function when it is first administered within less than 24 hours after the induction of renal failure [10, 12–16]. Whether rhIGF-I will enhance recovery when it is first administered following a longer interval after the onset of ARF has not been previously tested. Thus, it is possible that in this study the lack of improvement in renal function with rhIGF-I may be due to the delay in inauguration of treatment.

Chronic renal failure induces resistance to the actions of rhIGF-I in both rats and humans [29, 30, 35], and it is possible that this resistance also occurs in ARF and contributes to the lack of effect of the recombinant peptide in this study. However, the actions of rhIGF-I are reduced, but not abolished in chronic renal failure [29, 30]. Moreover, in rats with ARF, rhIGF-I enhances the

recovery of renal function at plasma levels similar to those observed in the patients in the current study [13].

The biological actions of IGF-I are also influenced by seven IGF-binding proteins (IGFBPs) as well as the IGF-I receptor [36]. In this study, IGFBP-3, which is the major carrier for serum IGF-I, was much reduced below normal levels in sera from patients receiving either rhIGF-I or placebo (Fig. 4). In studies of rhIGF-I in patients with chronic renal failure, reduced serum IGFBP-3 levels have been associated with a loss of effect of rhIGF-I [37]. Thus, the fact that serum IGFBP-3 levels were very low from the onset of the study may have contributed to a lack of effect of IGF-I on the recovery from ARF.

Patients who were oligoanuric at baseline and who received rhIGF-I tended to have slower rates of improvement in urine output as well as in GFR and creatinine clearance compared with the respective placebo-treated subjects (Fig. 1B, 2B, and 3B). Although the differences were not statistically significant, this finding gives rise to the possibility of adverse effects of rhIGF-I on renal function in patients with ARF who are anuric or oliguric. The mechanisms of this possible effect of rhIGF-I cannot be discerned from this study. This potential adverse outcome also prohibited rhIGF-I dose-escalation studies.

Although the patients given rhIGF-I did not show any improvement in nutritional status, the data bearing on this question are difficult to interpret. First, the lack of difference in SUN levels between the rhIGF-I and placebo groups may reflect the effects of nutrient intake, degrees of catabolic stress, or dialysis regimens during the course of the study. Also, serum albumin and transferrin are negative acute phase proteins. Hence, the lack of difference in serum concentrations of either of these proteins with rhIGF-I therapy may reflect the effect of the catabolic stress of the associated illnesses. Thus, these data do not allow for an evaluation of whether rhIGF-I induced an anabolic effect in these patients.

The negative results in this study are consistent with one other clinical trial of rhIGF-I in ARF. Franklin et al, in a single-center study, administered rhIGF-I or placebo in random order to patients after surgical repair of abdominal aortic aneurysms [38]. In this latter trial, treatments were commenced shortly after completion of the surgery and were given to all patients, independently of whether patients had ARF and/or normal or increased serum creatinine at this time. The incidence of ARF was not significantly different in the rhIGF-I– or placebo-treated groups, and none of the subjects required renal replacement therapy. In this study, patients receiving rhIGF-I had a slightly increased serum creatinine clearance by day 3 of the study compared with patients treated with placebo. However, there was no difference in serum creatinine levels at discharge and in the length of hospital stay.

In summary, despite ample studies in research animals that indicated that rhIGF-I accelerates the rate of recovery of renal function in experimental ARF, this multicenter, prospective, randomized, and placebo-controlled trial fails to demonstrate that rhIGF-I has similar effects in patients with established ARF.

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