Insulin-like growth factor I improves renal function in patients with end-stage chronic renal failure

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George M. O'Brien Kidney and Urologic Diseases Center, Renal Division, Department of Internal Medicine and Cell Biology and Physiology, Washington University School of Medicine, St. Louis, Missouri 63110

Vijayan, Anitha, Samuel C. Franklin, Terry Behrend, Marc R. Hammerman, and Steven B. Miller. Insulin-like growth factor I improves renal function in patients with end-stage chronic renal failure. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R929–R934, 1999.—There is no pharmacological treatment to increase the glomerular filtration rate in end-stage renal disease (ESRD). The administration of 100 µg/kg of insulin-like growth factor (IGF-I) twice a day to patients with ESRD increases inulin clearance. However, its effect is short-lived and IGF-I has major side effects when given this way. To assess whether the use of a lower intermittent dose of IGF-I would effect sustained improvement of renal function with tolerable side effects we performed 1) a prospective open-labeled 24-day trial in which we enrolled five patients and 2) a 31-day randomized, double-blinded, placebo-controlled trial in which we enrolled 10 patients. Patients with ESRD [creatinine clearance of <15 ml·min⁻¹·(1.73 m²)⁻¹] and scheduled to initiate renal replacement therapy received subcutaneous IGF-I, 50 µg·kg⁻¹·day⁻¹, or vehicle. Treatment with IGF-I resulted in significantly increased glomerular filtration rates (inulin clearances) during the 3rd and 4th wk of therapy in both prospective and double-blinded studies. Vehicle had no effect. No patient required discontinuation of drug secondary to side effects. We conclude that IGF-I effects sustained improvement of renal function (clearances comparable to those generally achieved by dialysis) in patients with ESRD and is well tolerated.

dialysis; glomerular filtration rate; growth factor; middle molecules

Regardless of its etiology, the natural history of chronic renal failure is one of relentless progression to end-stage renal disease (ESRD). There is no pharmacological treatment for ESRD. The only therapeutic options are dialysis or transplantation (2, 12).

We have demonstrated that treatment of patients with moderate renal insufficiency [inulin clearance 21.9–55.1 ml·min⁻¹·(1.73 m²)⁻¹] (18) or advanced chronic renal failure [inulin clearance 5.1–20.6 ml·min⁻¹·(1.73 m²)⁻¹] (17) with subcutaneous insulin-like growth factor (IGF-I) (100 µg/kg twice a day) improves renal function. Unfortunately, the effectiveness of therapy in ESRD was limited by the development of intolerable side effects and tachyphylaxis manifest after 7 days (17).

Such problems with IGF-I administration are not unique to our experience. The incidence of IGF-I side effects is related directly to the magnitude of the dose (11, 15). The transient nature of the beneficial effects of IGF-I has been observed in other settings. For example, improvement of nitrogen balance in patients with acquired immunodeficiency syndrome (AIDS) is observed in patients that receive IGF-I (48 µg·kg⁻¹·day⁻¹), but the effect is lost after 7 days when the growth factor is administered every day.

Ike et al. (10) administered a dose of subcutaneous IGF-I lower than that employed by us (17, 18) (60 µg/kg twice a day) for 30 days to eight patients with baseline inulin clearances of 8–27 ml·min⁻¹·(1.73 m²)⁻¹. Two patients dropped out of their study for reasons deemed to be unrelated to IGF-I therapy. With IGF-I treatment there was a modest (14%) increase in the average glomerular filtration rate, which approached statistical significance. Inulin clearance was elevated significantly compared with baseline only on day 4 of IGF-I therapy.

The present study was conducted to determine whether IGF-I can effect sustained improvements of renal function with a tolerable level of side effects. To this end, 15 patients with advanced, symptomatic chronic renal failure were administered IGF-I or vehicle. We used a dose (50 µg·kg⁻¹·day⁻¹) lower than that used previously by us (17, 18) in 1) a prospective open-labeled trial and 2) a randomized, double-blinded, placebo-controlled trial, in hopes of reducing the incidence of side effects. Patients received the growth factor on a schedule of 4 days on drug followed by 3 days off drug in hope that intermittent administration would eliminate tachyphylaxis.

Our data are the first to demonstrate that the administration of IGF-I to patients with ESRD results in a sustained improvement in renal function over a 31-day period of time to a level that is comparable to that generally achieved by any type of chronic dialysis and is well tolerated.

METHODS

Patients were recruited from the Washington University Renal Clinic and from nephrologists in the St. Louis area. Characteristics of the patients, including baseline inulin clearances, are shown in Table 1.

Entry criteria for all patients included age >18 years, a creatinine clearance of <15 ml·min⁻¹·(1.73 m²)⁻¹ measured within the previous 6 mo, and a history negative for cancer within the previous 5 years. Inclusion in our study was an alternative to the initiation of dialysis that had to be accept-

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Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient Age/Sex</th>
<th>Diagnosis</th>
<th>Medications</th>
<th>Inulin Clearance, ml·min⁻¹·(1.73 m²)⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>71/F</td>
<td>DM</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50/M AdPKD</td>
<td>DM</td>
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</tr>
<tr>
<td>3</td>
<td>59/F</td>
<td>Chronic GN</td>
<td>E, G</td>
</tr>
<tr>
<td>4</td>
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<td>A, D, D, G, H, J</td>
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<tr>
<td>5</td>
<td>64/F</td>
<td>Chronic GN</td>
<td>A, C, D, F, H, J, M</td>
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<tr>
<td>Double-blinded placebo-controlled randomized study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-I 1</td>
<td>47/F</td>
<td>DM</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>72/F</td>
<td>HTN</td>
<td>A, C, F, I, J, P, N</td>
</tr>
<tr>
<td>3</td>
<td>66/M</td>
<td>DM</td>
<td>A, C, G, J, N, Q</td>
</tr>
<tr>
<td>4</td>
<td>51/F</td>
<td>DM</td>
<td>A, C, D, G, I, J</td>
</tr>
<tr>
<td>5</td>
<td>32/F</td>
<td>DM</td>
<td>B, D, I, P</td>
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<tr>
<td>Vehicle 1</td>
<td>58/M</td>
<td>HTN</td>
<td>A, B, G, J</td>
</tr>
<tr>
<td>2</td>
<td>72/M</td>
<td>DM</td>
<td>A, D, E, G, I</td>
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<tr>
<td>3</td>
<td>79/M</td>
<td>DM</td>
<td>C, E, G, J, K, Q</td>
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<tr>
<td>4</td>
<td>55/M</td>
<td>DM</td>
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<tr>
<td>5</td>
<td>47/F</td>
<td>DM</td>
<td>C, D, G, I, P, Q</td>
</tr>
</tbody>
</table>

Medications are A, angiotensin converting enzyme inhibitor; B, β-blocker; C, calcium channel blocker; D, loop diuretic; E, erythropoietin; F, iron; G, calcium; H, 3-hydroxy-3-methylglutaryl CoA reductase inhibitor; I, insulin; J, sodium bicarbonate; K, sulfonylurea; L, digoxin; M, warfarin; N, nitrates; O, 1,25-di-OH vitamin D; P, α-blocker; Q, clopidogrel; ADPKD, autosomal dominant polycystic kidney disease; DM, diabetes mellitus; F, female; GN, glomerulonephritis; HTN, hypertension; M, male; IGF, insulin-like growth factor.

able both to the patients and to their nephrologists and that was subject to continuous review by the latter. Three patients enrolled in the prospective study had functioning arterial-venous grafts, and two patients had planned to initiate peritoneal dialysis. Five patients in the randomized study had functioning arterial-venous grafts, two patients had planned to initiate peritoneal dialysis, and three were awaiting access placement.

Blood pressure was adequately controlled in all patients, and there was no evidence of acute intercurrent illness in any patient. Patients with absolute indicators for dialysis, such as acidosis, hyperkalemia, pericarditis, mental status changes, or fluid overload intractable to diuretic therapy, were excluded from the study.

The study protocols were approved by the Human Studies Committee of Washington University. On admission to the General Clinical Research Center (GCRC) patients underwent a physical examination, and laboratory studies were obtained as shown in Table 2. In addition, serum was obtained and stored at −70°C for measurements of levels of total IGF-I and IGF binding proteins 1–3 (IGFBP-1–3; Endocrine Sciences, Calabasas Hills, CA). Renal function was evaluated by measuring the clearance of exogenous insulin. As before (17, 18), values represent the mean of three 1-h clearances. Patients received recombinant human IGF-I (rIGF-I) or vehicle (provided by Genentech, South San Francisco, CA) 50 µg/kg sc for 4 consecutive days followed by 3 days off drug or vehicle (first 4 days were days 0, 1, 2, and 3). Participants in the studies remained in the GCRC for 4 days to be observed for side effects and to learn self-administration of the IGF-I or vehicle. Thereafter, these agents were self-administered by participants as outpatients.

The prospective, open-labeled study was designed to be conducted for 24 days with five patients enrolled. The above-mentioned studies were obtained on the 1st and 4th day of each week for the first 4 wk. Patients who manifest an improvement in inulin clearance in the prospective study were invited to remain on IGF-I therapy after the initial period of study. In these patients all the laboratory studies were repeated on the 6th, 8th, 12th, 16th, 20th, 26th, 36th, 52nd, and 73rd wk.

The randomized, double-blinded, placebo-controlled study was designed to be conducted for 45 days with five patients enrolled in each group. Renal function studies were obtained on the 1st and 4th day of weeks 1, 3, and 5. Patients remained on placebo or IGF-I for 31 days and received no therapy for the next 14 days.

Data are expressed as means ± SE. Results of insulin clearances, IGF-I and IGFBP-3 levels, and electrolytes were compared at each time point to baseline by Dunnett's multiple comparison test (7). Student-Newman-Keuls multiple comparisons test was used when comparing between groups in the randomized trial. Significance was defined as a P value <0.05 for two-tailed analysis.

RESULTS

The baseline inulin clearance for the five subjects enrolled in the prospective (open labeled) study was 7.8 ± 0.8 ml·min⁻¹·(1.73 m²)⁻¹. Compared with baseline, the clearance was significantly elevated at days 14, 17, 1, and 24 as illustrated (Fig. 1A). The inulin clearance was 177% of baseline on day 17 and 154% of baseline on day 24 of therapy.

The mean of all values for serum IGF-I obtained after 4 days on IGF-I (days 3, 10, 17, and 24; 302.6 ± 13.2 ng/ml) was significantly higher than the mean of all values after 3 days off IGF-I (days 0, 7, 13, and 21; 151.6 ± 14.3 ng/ml; P < 0.001, Student's t-test). This is in contrast to the progressive decline in levels of circulating total IGF-I that occurred over time during administration of 100 µg/kg IGF-I twice per day (17).

Levels of IGFBP-3 were within the normal range for the assay employed (1.9–3.6 mg/l) at baseline, and no value was significantly different from baseline during the 24 days of therapy (Fig. 1C). This is in contrast to the fall that occurred over time during therapy with the higher dose we previously employed (17). Levels of

Table 2. Effect of IGF-I on serum and urine parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>IGF-I (Day)</th>
</tr>
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<tbody>
<tr>
<td>Serum Na⁺, mg/dl</td>
<td>139 ± 0.5</td>
</tr>
<tr>
<td>Serum K⁺, mg/dl</td>
<td>3.6 ± 0.3</td>
</tr>
<tr>
<td>Serum HCO₃⁻, meq/l</td>
<td>23 ± 3.2</td>
</tr>
<tr>
<td>Serum calcium, mg/dl</td>
<td>9.9 ± 0.2</td>
</tr>
<tr>
<td>Serum phosphate, mg/dl</td>
<td>5.6 ± 0.7</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>74 ± 9.1</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>6.5 ± 1.5</td>
</tr>
<tr>
<td>Urine volume, ml/24 h</td>
<td>2,639 ± 692</td>
</tr>
<tr>
<td>Urine calcium, mg/24 h</td>
<td>65 ± 32</td>
</tr>
<tr>
<td>Urine phosphate, mg/24 h</td>
<td>537 ± 88</td>
</tr>
<tr>
<td>%Tubular reabsorption of phosphate</td>
<td>61 ± 5</td>
</tr>
<tr>
<td>Urine protein, mg/24 h</td>
<td>1,115 ± 154</td>
</tr>
</tbody>
</table>

Data are shown as means ± SE. Values were obtained on day 0 before insulin-like growth factor I (IGF-I) administration (baseline) or on day 24 after IGF-I administration was completed. BUN, blood urea nitrogen. *P < 0.05, drug treatment vs. baseline (Student's t-test).
IGFBP-1 measured at baseline on day 0 (26.3 ± 6.1 ng/ml) were within the normal range for the assay employed (10–150 ng/ml) and were not significantly changed by the administration of IGF-I (data not shown).

Levels of IGFBP-2 (2,005 ± 809 ng/ml) were well above the normal range for the assay employed (225–1,038 ng/ml). As was the case for total IGF-I, the mean of all values obtained after 4 days on IGF-I (days 3, 10, 17, and 24; 2,464 ± 104 ng/ml) was significantly higher than the mean of all values after 3 days off IGF-I (days 0, 7, 13, and 21; 1,862 ± 56 ng/ml; P < 0.01, Student’s t-test).

The incidence and severity of side effects were reduced in patients in the present study compared with our previous experience (17). One patient developed peripheral edema, and two others experienced local irritation at the site of drug injection. No patient receiving 50 µg·kg⁻¹·day⁻¹ of IGF-I intermittently required discontinuation of drug therapy because of the development of side effects (or for any other reason), in contrast to four of five patients receiving 100 µg/kg twice a day in our previous trial (17).

Four of five patients continued on IGF-I after the initial 24 days of treatment. Patient 1 elected to discontinue IGF-I and remained off dialysis for an additional 2 mo. Patients 2 and 3 remained off dialysis until they received kidney transplants at weeks 18 and 32, respectively. Patient 4 began dialysis at 10 wk postinitiation of IGF-I therapy. Patient 5 remained on IGF-I therapy for 20 mo. Levels of inulin clearance measured over time in this patient are shown in Fig. 2. Clearances remained elevated compared with baseline for 18 mo.

As in our studies employing higher doses of IGF-I (17, 18), administration of low-dose intermittent IGF-I had no significant effect on serum Na⁺, K⁺, HCO₃⁻, calcium, or phosphate concentrations or on urine volume, urine calcium, urine Na⁺, or urine protein excretions. Levels of blood urea nitrogen and creatinine did not change significantly. The percent tubular reabsorption of phosphate was significantly increased as before (17, 18; Table 2).

We showed previously that the administration of vehicle for 4 days to patients with ESRD has no effect on inulin clearances (17). To examine the effects of IGF-I and vehicle over a longer period of time in a double-blinded fashion, intermittent IGF-I or intermittent vehicle was administered to five patients each in a randomized double-blinded trial. Values for baseline inulin clearance did not differ significantly between vehicle-treated [10.8 ± 1.6 ml·min⁻¹·(1.73 m²)⁻¹] and IGF-I-treated patients [7.6 ± 0.4 ml·min⁻¹·(1.73 m²)⁻¹].

Patient 5 in the vehicle-treated group began dialysis on day 10, and patient 5 in the IGF-I-treated group began dialysis on day 16. In these patients, vehicle or IGF-I was stopped at the time of initiation of dialysis. Data originating from these patients generated up until the time of dialysis are included in Fig. 3.
Compared with baseline, the inulin clearance was significantly elevated at days 17 and 31 in IGF-I-treated patients (Fig. 3). The inulin clearance was 141% of baseline on day 17 [10.7 ± 0.8 ml·min⁻¹·(1.73 m²)⁻¹] and 150% of baseline on day 31 of therapy [11.4 ± 0.9 ml·min⁻¹·(1.73 m²)⁻¹]. By 2 wk after discontinuation of IGF-I (45 days), inulin clearance was no different than that measured at baseline [9.7 ± 0.7 ml·min⁻¹·(1.73 m²)⁻¹]. In contrast to IGF-I, the administration of vehicle had no effect on inulin clearance (Fig. 3). Compared with the placebo-treated patients, those patients receiving IGF-I had significantly increased clearances on days 17, 28, 31, and 45.

The incidence and severity of side effects in the double-blind study were similar to those in the prospective study. One patient developed transient jaw pain in the IGF-I-treated group, which was self-limited. There were no side effects in the placebo-treated group. No patient in either group required discontinuation of therapy because of the development of side effects.

Administration of IGF-I or vehicle did not affect serum electrolytes, blood pressures, or body weights (not shown).

**DISCUSSION**

IGF-I enhances rates of single-nephron glomerular filtration in rats secondary to its action on the glomerular vasculature and is a growth promoter for the proximal nephron in rodents (10, 17, 18). Because it can increase the glomerular filtration rate in humans even in the setting of near-ESRD, its therapeutic use has been proposed for patients with chronic renal failure (10, 17, 18).

In our previous study, patients received 200 µg·kg⁻¹·day⁻¹ of rhl GF-I. Although an initial increase in inulin clearance was observed in the IGF-I-treated patients, the effect was not sustained beyond 7 days of therapy and four of five patients developed side effects requiring discontinuation of IGF-I. Two individuals developed pericarditis, one Bell’s palsy, and one gingival hypertrophy (17).

The dose of IGF-I used in the present studies was lower, and the growth factor was administered on an intermittent basis. Patients experienced an increase in inulin clearance that was comparable to that demonstrated in our previous study (17). However, in contrast to previous results, the effect was sustained for 24 (Fig. 1A) or 31 days (Fig. 3), so long as the patients continued receiving IGF-I. In addition, no patient developed side effects that required discontinuation of therapy.

Our prospective trial was designed for 24 days. However, four patients elected to remain on IGF-I after the trial was completed. As noted, no patient enrolled in our trial had an “absolute” indication for dialysis. However, initiation of dialysis within the next several weeks had been recommended to all patients who participated in our study by their nephrologist before enrollment. Dialysis was initiated in one patient who continued to receive IGF-I 10 wk after our study was completed and was initiated in another 20 mo after the study’s completion (Fig. 2). Two patients who remained on IGF-I never initiated dialysis and received renal transplants at 18 and 32 wk, respectively. The patient who elected to discontinue IGF-I began dialysis 8 wk after completion of the study.

The basis for the tachyphylaxis to the higher dose of IGF-I used in our previous study is unclear. The interactions of IGF-I with sensitive tissues are complex. IGF-I circulates in tight noncovalent association with IGFBPs, which both enhance and inhibit IGF-I actions (6). In addition, IGFBPs present in tissues regulate the interactions of circulating IGF-I with its receptor (4, 14). In kidney, the number of IGF-I receptors is inversely related to levels of circulating IGF-I (9).

The pharmacokinetics of IGF-I in ESRD are largely unaltered, apart from a reduction in the total IGF-I volume of distribution (19). However, administration of IGF-I to patients with normal renal function (8) or ESRD (17) has been accompanied by changes in at least one component of the IGF-I effector system, a reduction in circulating levels of IGFBP-3.

IGFBP-3 is a component of the complex to which most circulating IGF-I is bound (6). Because the synthesis of IGFBP-3 is stimulated by growth hormone, the reduction in circulating IGFBP-3 that accompanies IGF-I administration is thought to result, at least in part, from inhibition of growth hormone release by exogenous IGF-I (6).

In the current study, there was no reduction in the levels of circulating IGFBP-3 and no evidence of tachyphylaxis developing over time. It is possible that the lack of persistence of the action of IGF-I to enhance inulin clearance in our previous study represented a refractoriness that resulted directly from the change in...
IGFBP-3 or that was reflected by this change in IGFBP-3. A similar refractoriness to the anabolic action of IGF-I with a concomitant decrease in IGFBP-3 levels was observed in cachectic patients with AIDS (15). Also similar are the findings of Ike et al. (10), who administered 60 µg/kg IGF-I twice per day to patients with ESRD (10). At this dose (4 times the weekly dose we employed), IGF-I increased inulin clearance only on day 4 of a 30-day course of therapy. Levels of total IGF-I and of free IGF-I increased approximately sixfold over baseline, peaking on days 10–30. However, levels of IGFBP-3 fell during therapy, reaching a nadir on day 15.

Perspectives

There is no effective drug therapy to enhance renal function in the setting of advanced chronic renal insufficiency. Dialytic therapy, although lifesaving, is expensive, time-consuming, and places patients at risk for a variety of complications. Often, the placement of vascular access must occur immediately and hemodialysis must be initiated precipitously (3, 13). Many patients would benefit from a medical therapy that could extend the period of time in which their own kidneys functioned adequately.

Both prospective and randomized, double-blinded, placebo-controlled studies demonstrate that the exogenous administration of IGF-I to patients with ESRD can induce a sustained improvement in renal function. The long-term improvement in renal function effected by IGF-I in the prospective study is the first to achieve statistical significance. Our randomized, double-blinded, placebo-controlled trial is the first to demonstrate that the administration of IGF-I to patients with ESRD can induce a sustained improvement in renal function. Although renal function was not restored to normal by IGF-I, the increases in inulin clearance in IGF-I-treated patients occurred over an important range. The clearances before beginning IGF-I in patients participating in both prospective and double-blinded studies were less than clearances of patients with ESRD on dialysis. However, at the termination of both studies, on days 24 or 31 of IGF-I therapy, clearances were comparable or higher than those generally achieved by any means of standard chronic dialytic therapy (16). An additional theoretical benefit of IGF-I over dialysis would be the more effective removal of "middle molecules" that would be accomplished by the patients' native kidneys compared with dialysis membranes (16).

The use of IGF-I in humans is not without risk, including that of malignancy (5). Although any risk of cancer is of concern, such a risk in patients with ESRD must be weighed against the fact that the mortality for males during the first year of treatment for ESRD is 27%, and the expected remaining lifetimes for all patients who develop ESRD between ages 45–54 and 55–64 are 6.9 and 5.3 years, respectively (2).

No firm conclusions can be made on the basis of this small number of patients. However, an argument can be made that IGF-I might delay the need for renal replacement therapy. A double-blinded, placebo-controlled, randomized trial will be required to determine whether this is the case.

The authors are grateful to all the patients involved in our studies and to the referring nephrologists.

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