ANNALS OF SURGERY
Vol. 228, No. 4, 439–448

Growth Hormone Treatment In Pediatric Burns

A Safe Therapeutic Approach

Roque J. Ramirez, MD, Steven E. Wolf, MD, Robert E. Barrow, PhD, and David N. Herndon, MD

From the Department of Surgery, University of Texas Medical Branch and Shriners Burns Hospital-Galveston

Objective

To determine the safety and efficacy of recombinant human growth hormone (*rhGH*) in the treatment of children who are severely burned.

Summary Background Data

During the last decade, we have used recombinant human growth hormone (*rhGH;* 0.2 mg/kg/day SQ) to successfully treat 130 children with more than 40% total body surface area (TBSA) burns to enhance wound healing and decrease protein loss. A significant increase in the mortality of adult patients in the intensive care unit who were given *rhGH* has recently been reported in two large European trials which questions the therapeutic safety of *rhGH.*

Methods

The records of 263 children who were burned were reviewed. Patients receiving either *rhGH* at 0.2 mg/kg/day subcutaneously as part of a randomized clinical trial (n = 48) or therapeutically (n = 82) were compared with randomized placebo-administered controls (n = 54), contiguous matched controls (n = 48), and matched patients admitted after August 1997, after which no patients were treated with *rhGH* (n = 31). Morbidity and mortality, which might be altered by rhGH therapy, were considered with specific attention to organ function or failure, infection, hemodynamics, and calcium, phosphorous, and albumin balance.

Results

A 2% mortality was observed in both *rhGH* and saline placebo groups in the controlled studies, with no differences in septic complications, organ dysfunction, or heart rate pressure product identified. In addition, no difference in mortality could be shown for those given *rhGH* therapeutically *versus* their controls. No patient deaths were attributed to *rhGH* in autopsies reviewed by observers blinded to treatment. Hyperglycemic episodes and exogenous insulin requirements were higher among *rhGH* recipients, whereas exogenous albumin requirements and the development of hypocalcemia was reduced.

Conclusions

Data indicate that *rhGH* used in the treatment of children who were severely burned is safe and efficacious.

Recombinant human growth hormone (*rhGH*) has been shown to have beneficial anabolic effects in treating patients after major surgery,[1,2] trauma,[3] sepsis,[4,5] and burns.[6] The rationale for treating these hypercatabolic patients with *rhGH* includes improved muscle protein synthesis and accelerated wound healing. We have treated children who were severely burned with *rhGH* for more than 10 years and have reported that 0.2 mg/kg/day accelerated donor site wound healing by up to 30%,[7,8] enhanced basal lamina coverage, and increased collagen types IV and VII, laminin, and cytokeratin-14 in the skin donor sites.[9] All of these improve wound integrity. These beneficial changes were associated with a 25% reduction in hospital stay and costs.[10,11] We have also shown that *rhGH* increased protein synthesis by more than 25% and improved protein balance in catabolic burn patients, presumably via an observed increase in serum IGF-1 levels.[12] Other studies have shown that *rhGH* causes significant serum elevations in total catecholamines, norepinephrine, epinephrine, insulin, glucagon, free fatty acids, and increased blood flow across the leg.[13]

In a recent report of two Phase III prospective, randomized, double-blind, placebo controlled trials conducted in Europe, the effects of *rhGH* (n = 259) given to critically ill adult intensive care unit patients exclusive of burns were compared with those receiving a placebo (n = 264). This

Presented at the 118th Annual Meeting of the American Surgical Association, April 3, 1998, Palm Beach, Florida.
Address correspondence and reprint requests to David N. Herndon, MD, Shriners Burns Hospital-Galveston, 815 Market, Galveston, TX 77550.
Supported by SHC grants 8660 and 8770, NIH grants 5T32GM08256-07 and 1RO1GM56687-01, and by Genentech grants M0010 and M0353.
Accepted for publication December 1, 1997.

report disclosed a significant increase in mortality among catabolic patients treated with *rhGH,* such that 42% of the *rhGH*-treated patients died in comparison with an 18% mortality in the placebo group.[14] The potential for deleterious effects in the pediatric patient who was critically injured thus prompted a new investigation at our burn center to determine whether *rhGH* is safe in the pediatric burn population.

MATERIALS AND METHODS

Patient Population and Parameters Studied

One hundred two severely burned children were entered into a randomized prospective, double-blind study comparing the effects of 0.2 mg/kg/day SQ *rhGH* with saline placebo. Inclusion parameters for the controlled studies were age 1 to 18 years, admitted within 3 days of injury to our pediatric burn center between 1988 and 1998, and whom had sustained a more than 40% total body surface area (TBSA) burn with a third-degree burn more than 10% requiring at least one donor site. Therapeutic *rhGH* was often given to younger and sicker children admitted to our burn center (n = 82), many of whom were admitted more than 8 days postburn. The majority of these patients were transferred from Mexico or South America, malnourished, with varying degrees of infection. These patients were compared with 48 contiguous controls matched for age, sex, and burn size. Another 31 children admitted to our burn center after August 1997 with burns covering more than 40% TBSA with more than 10% third-degree and who required skin grafting were also used as controls. Growth hormone was electively stopped during this period due to the findings of the European trials. Patient records were reviewed to examine the effects of *rhGH* on overall morbidity and mortality, focusing on the incidence of infectious, renal, cardiac, and respiratory complications. To obviate potential variables affecting additional parameters, analyses of glucose kinetics, insulin requirements, electrolyte homeostasis (particularly calcium and phosphorous), cardiac rate and blood pressure, and albumin requirements were performed in the blinded randomized groups.

Morbidity and Mortality

The records of all patients receiving *rhGH* therapeutically or in randomized controlled trials, and all matched control populations were reviewed for mortality and drug-related morbidity. A pediatrician and pathologist, blinded to treatment, reviewed all patient autopsies focusing on any morbidity that could be attributed to the use of *rhGH.* Survivors were compared with nonsurvivors, and each patient was reviewed for the development of organ failure and sepsis. Renal failure was defined as serum creatinine greater than 2.0 mg/dl with urine output less than 1 ml/kg/hr for 2 days or more. Patient ventilatory requirements were assessed. Cardiac dysfunction was measured in terms of hemodynamic effects or cardiac arrest, with arrest being defined as a pulseless arrhythmia requiring mechanical and chemical resuscitation to successfully restore cardiac activity compatible with life using established Pediatric Advanced Life Support protocols. Sepsis was defined as isolation of a septic source [pathogenic bacteria or fungus on blood culture; wound biopsy with more than 10^5 organisms/g tissue; urinary tract infection with more than 10^5 organisms/ml urine; or pulmonary infection with positive bacteria and white cells on $\geq$ Class III sputum], and 5 or more clinical sepsis criteria which include tachypnea, prolonged paralytic ileus, hypo- or hyperthermia ($<36.5°$ or $>38.5°C$), altered mental status, thrombocytopenia (<50 K platelets/mm^3), leukopenia or leukocytosis (<3.5 or $>15.0 \times 10^3$ cells/mm^3), unexplained acidosis, or hyperglycemia.

Albumin Requirements

Serum albumin concentrations were measured daily. Patients with albumin concentrations less than 2.5 g/dl received 6.25 g/day exogenous albumin for children less than 2 years of age, 12.5 g/day for children 2 to 9 years old, and 25 g/day for children 10 to 18 years old to maintain colloid osmotic pressures. Total albumin required each day during acute hospitalization was recorded for each patient within the randomized study groups. Total albumin infused and grams of albumin infused per $meter^2$ burn were compared. Percent caloric goals and percent protein goals, defined as: 2100 Kcal M_2 TBSA + 1000 Kcal M_2 burned/ 24 hours and 3 to 4 g protein/kg for infants, 1800 Kcal M_2 TBSA + 1300 Kcal M_2 and 120: 1 kcal to gram nitrogen ratio for children 1 to 12 years old, and 1500 Kcal M_2 TBSA + 1500 Kcal M_2 and 120: 1 kcal to gram nitrogen ratio for children more than 12 years old, were also compared.

Glucose/Insulin Kinetics

Hyperglycemia (five or more episodes of serum glucose >250 mg/dl) and insulin requirements were assessed for randomized study patients during acute hospitalization. Patients were given insulin to maintain euglycemia of less than 150 mg/dl. The incidence of hyperglycemia and daily insulin requirements in those requiring exogenous insulin were compared.

Electrolytes

Serum ionized calcium and total serum phosphorous were measured daily. Calcium gluconate and potassium phosphate were given intravenously to correct low values. Normocalcemia and normophosphatemia were defined as 4.5 to 5.3 ionized calcium and 2.5 to 5.5 mg/dl phosphorous. The incidence of abnormal serum ionized calcium and phosphate and total calcium gluconate sup-

Table 1. PATIENT DEMOGRAPHICS AND MORTALITY

Patient Groups	n	Age (Years)	Female:Male Ratio	% TBSA	% 3rd	% Mortality
Randomized study (*rhGH*, 0.2 mg/kg/day)	48	7 ± 1	1:1.5	59 ± 3	47 ± 3	2
Randomized study placebo	54	8 ± 1	1:2.2	62 ± 2	51 ± 3	2
Therapeutic (*rhGH*, 0.2 mg/kg/day)	82	6 ± 1	1:1.8	61 ± 3	50 ± 3	10
Contiguous controls (No *rhGH*)	48	7 ± 1	1:1.6	62 ± 2	52 ± 3	17
Controls admitted after August 1997 (No *rhGH*)	31	8 ± 1	1:1.7	60 ± 4	43 ± 6	13

TBSA = total body surface area.
Data presented as Means ± SEM.

plementation requirements were compared between randomized study groups.

Hemodynamic Effects

The effects of *rhGH* treatment on myocardial energy expenditure in pediatric patients with burns using noninvasive measurements of rate-pressure product and heart rate were evaluated. Rate-pressure products and heart rates were recorded at baseline before onset of growth hormone therapy (after adequate fluid resuscitation) and at weekly intervals thereafter until the cessation of growth hormone therapy. All values and measurements were made at the same time of the day (7:00 AM) to ensure uniformity and obviate the effects of extraneous daytime activities on the parameters being studied. The 102 patients enrolled in the randomized controlled trial were evaluated using the following standards for overall resting and supine mean rate-pressure products (mm Hg · beats/min × 10^{-3}): 1) children 2 to 6 years of age: boys 9125 ± 1503 and girls 9356 ± 1618; 2) children 6 to 12 years of age: boys 8825 ± 1306 and girls 9036 ± 1437; and 3) children 12 to 17 years of age: boys 7994 ± 1737 and girls 8925 ± 1955. Patients treated with beta-adrenergic blocking agents during their acute hospitalization were excluded from this investigation to eliminate confounding variables that might effect myocardial oxygen consumption and cardiac work. Data collected were analyzed by two-way ANOVA with repeated measure analysis performed within groups.

Data Analysis/Statistics

ANOVA or Chi-square analysis, with the Yates continuity correction applied to the 2 × 2 tables were used when appropriate to compare treatment and placebo groups. When significant interactions of main effects occurred, unpaired Student's t test was used post hoc to assess significant differences. Differences were considered significant at $p < 0.05$ unless otherwise designated. Values are expressed as means ± SEM.

RESULTS

Mortality

Patient demographics and mortality are presented in Table 1. Mortality was not significantly different in children receiving *rhGH* for salvage (10%) compared with combined contiguous and subsequent non*rhGH* treated controls (15%) or randomized study groups. No significant differences in mortality could be shown between patients treated with *rhGH* in the randomized study compared with placebo (2% *versus* 2%). There were 22 deaths in the 263 children studied. The use of *rhGH* could not be determined to be a direct or associated cause of death in any patient assessed by our blinded reviewers. The individual causes of death are presented in Table 2. Recognized clinically as a high mortality risk group, fatalities were greatest among those children less than 3 years in age with larger TBSA burns.

Morbidity

In our analysis of critical care related complications, no significant differences in the development of cardiac, renal, or septic events were shown between randomized study groups (Table 3). No significant differences in patient requirements for mechanical ventilatory support could be shown between surviving patients within groups.

Albumin Supplementation

Albumin supplementation to maintain near normal serum albumin concentrations was reduced by more than 50% in the randomized study patients receiving *rhGH*

Table 2. CAUSE OF DEATH IN BURNED CHILDREN

Patient Group	n	% TBSA	Age (years)	LOS (days)	*rhGH* (days)	Last Dose *rhGH* to Death (days)	Cause of Death
Study—*rhGH*	1	80	1.7	69	62	7	Ps. aeruginosa Sepsis, Bronchopneumonia, Inhalation Injury, Prolonged Respiratory Failure
Study—placebo	1	90	1.2	123	N/A	N/A	Inhalation Injury, Respiratory Insufficiency, Bronchopneumonia, Necrotizing Tracheobronchitis
Therapeutic (*rhGH*)	1	51	5.0	2	1	0	Acute Pneumomediastinum and Bilateral Pneumothoraces, Inhalation Injury
	1	95	2.8	4	2	0	Anoxic Brain Injury, Cerebral Swelling with Herniation, Inhalation Injury
	1	60	1.8	19	10	4	Severe Anaphylactoid Reaction to Vancomycin, Pulmonary Consolidation
	1	80	3.3	42	34	2	Diffuse Pulmonary Fibrosis from Prolonged Ventilatory Support, Bilateral Acute Tubular Necrosis
	4	(60–97)	(1.6–6.3)	(3–160)	(2–154)	0	Klebsiella Pneumonia, Septic Shock, Invasive Aspergillus Infection (1), Acute Pneumonitis with Respiratory Failure (2)
Therapeutic Controls (*No rhGH*)	4	(67–98)	(1.1–2.9)	(2–3)	N/A	N/A	Irreversible Burn Shock with extensive ATN, DIC, s/p Cardiac Arrest with Anoxic Brain Injury (2), Direct thermal injury to stomach and cerebral cortex (1)
	3	(62–80)	(1.1–18)	(1–12)	N/A	N/A	Burn Wound Sepsis and Pneumonitis with Pseudomonas aeruginosa, Severe ARDS, Ischemic Bowel Necrosis with Peritonitis (1)
	3	(40–90)	(5.1–3.1)	(10–31)	N/A	N/A	Disseminated Phycomycosis (1), Aspergillosis and Candidiasis (1) or Fusarium (1) Infections with Systemic Sepsis and Multi-organ Necrosis
	2	(58–78)	(1.8–0.6)	(2–26)	N/A	N/A	Severe Inhalation Injury and ARDS with Recurrent Pneumothoraces and Progressive Respiratory Failure

ARDS = Acute Respiratory Distress Syndrome; ATN = Acute Tubular Necrosis; DIC = Disseminated Intravascular Coagulopathy; LOS = Length of Hospital Stay.

compared with placebos that were matched in dietary intake, total body surface area, and burned surface area. This reduction was in both total grams of albumin given and total grams of albumin given per meter^2 burned (Table 4). All patients were given enteral diets with caloric intake calculated using weight-maintenance formulas.[15,16] No difference in weight accumulation could be distinguished between groups.

Table 3. INCIDENCE OF CARDIAC ARREST,* RENAL FAILURE, SEPSIS, VENTILATORY SUPPORT, AND DAYS ON VENTILATOR

Patient Groups	n	Cardiac Arrest (%)	Renal Failure (%)	Sepsis (%)	Ventilatory Support Required (%)	Ventilator Days in Surviving Patients†
Randomized study (rhGH, 0.2 mg/kg/day)	48	6	2	23	48	6.0 ± 0.1
Randomized study placebo	54	0	2	20	39	7.6 ± 1.7
Therapeutic (rhGH, 0.2 mg/kg/day)	82	7	2	34‡	40	6.7 ± 1.2
Therapeutic controls (no rhGH)	79	9	10	13	46	4.8 ± 1.3

* Cardiac rhythm and blood pressure restored after cardiopulmonary resuscitative efforts.
† Data presented as Means ± SEM.
‡ Significant difference *versus* Therapeutic Controls, $p < 0.01$.

Table 4. EFFECT OF *rhGH* ON ALBUMIN REQUIREMENTS IN BURNED CHILDREN

Patient Group	n	Dietary Intake: % Caloric Goals	Dietary Intake: % Protein Goals	Dietary Intake: % Dietary Fat	Body Surface Area: Total (m^2)	Body Surface Area: Burned (m^2)	Total Albumin (gm)	Albumin/m^2 Burn (gm/m^2)
Randomized study (*rhGH*, 0.2 mg/kg/day)	47	92 ± 2	84 ± 3	32 ± 2*	1.08 ± 0.08	0.66 ± 0.05	75 ± 9*	125 ± 15*
Randomized study placebo	52	94 ± 2	86 ± 2	38 ± 1	1.05 ± 0.06	0.65 ± 0.05	210 ± 29	375 ± 58

* Significant difference *versus* placebo, $p < 0.001$; Data presented as Means ± SEM.

Glucose and Insulin Kinetics

The incidence of hyperglycemia after burn injury was 41% in the randomized placebo treated patients compared with 63% of the children randomized to receive *rhGH*. A higher percentage (46% *vs.* 24%) of these children required exogenous insulin to maintain euglycemia, and the mean daily insulin requirements in those needing insulin also were significantly greater ($p < 0.05$) than placebo treated children (Table 5). Propranolol administration was not shown to effect glucose kinetics in these patients in a separate subset analysis.

Calcium and Phosphorous Homeostasis

Hypocalcemic episodes were significantly reduced from 87% to 69% ($p < 0.05$) in randomized study patients receiving *rhGH* when compared with placebo. As a consequence, less calcium supplementation was required in this group. No significant differences in the development of hypercalcemia, hypo- or hyperphosphatemia were shown between randomized study groups. A subset analysis of randomized patients receiving propranolol in conjunction with *rhGH* or placebo was conducted to examine contributing effects. No effect on calcium or phosphorous balance could be attributed to propranolol administration.

Hemodynamic Effects

All randomized study patients were found to have elevated rate-pressure products (over normal values when corrected for age) at baseline (12257 ± 424 mm Hg · beats/min × 10^{-3} in randomized *rhGH* patients and 11534 ± 456 mm Hg · beats/min × 10^{-3} for the placebo group). No difference in heart rate or rate-pressure products between groups at any of the time-points studied could be shown (Figures 1 and 2). Among the 19 of 48 *rhGH* recipients and 16 of 54 placebo patients treated with propranolol for tachycardia, no significant difference in hemodynamic profiles could be identified when analyzed with the respective randomized group or as a separate subset.

DISCUSSION

Two recent studies conducted in Europe reported an increase in mortality when *rhGH* was used therapeutically in severely ill adults in an intensive care setting. In our study, 48 severely burned children who received *rhGH* at 0.2 mg/kg/day SQ in a blinded study were compared with 54 burned children receiving placebo, and 82 patients treated therapeutically were compared with 79 non*rhGH*-treated controls to validate the safety of *rhGH* in the treatment of pediatric burns. The mortality in pediatric patients with major burns, admitted and randomized to receive *rhGH*

Table 5. HYPERGLYCEMIA & INSULIN REQUIREMENTS IN BURNED CHILDREN TREATED WITH *rhGH*

Patient Groups	n	% Hyperglycemia	% Requiring Exogenous Insulin	Insulin Requirements (units/day)
Randomized study (*rhGH*, 0.2 mg/kg/day)	48	63†	46†	32 ± 0.3*
Randomized study placebo	54	41	24	18 ± 0.1

* In patients requiring exogenous insulin only; data presented as Means ± SEM.
† Significant difference *versus* Control $p < 0.05$.

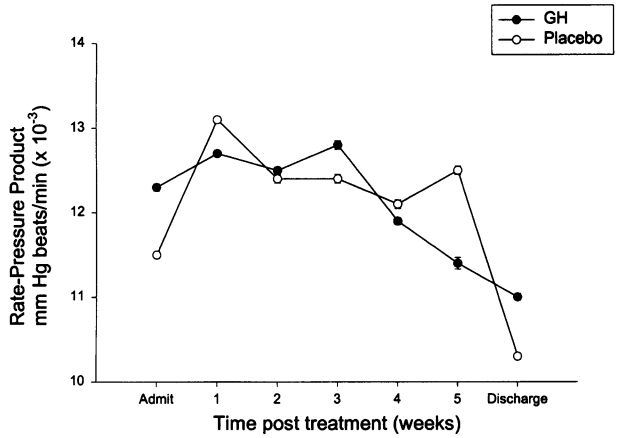

Figure 1. Schematic representation of changes in Rate-Pressure Product over hospital course in randomized study patients receiving either growth hormone (GH) or placebo. Data presented as means, bars are ±SEM.

within 72 hours of burn, was 2% (1 patient death). An identical mortality rate of 2% was observed in the randomized placebo treated group. Mortality in the patients treated with *rhGH* on a therapeutic basis was 10% (8 patient deaths). These patients would have been expected to have an increased mortality relative to the randomized study patients as a consequence of delays between burn injury and transfer to the burn unit for definitive treatment, young age, preexistent malnutrition, and infection.[17] These patients were selected to receive *rhGH* at the clinical discretion of the admitting attending physician. To examine the effects of *rhGH* in these salvage patients, we identified two additional control groups for comparison. The first group (n = 48) was composed of severely burned children that were admitted in the same time period, matched for age, sex, and burn size that were not placed on *rhGH* treatment by the admitting surgeon. The second control group consisted of all patients with burns more than 40% TBSA admitted to our burn center after August 1997 when *rhGH* administration was electively withheld as a treatment option. There were eight patient deaths in the contiguously treated group (17% mortality) and four deaths (13% mortality) in the later group, for a combined mortality rate of 15% in these control groups. No significant difference in patient mortality could be shown between these control groups and the therapeutic study group. We could find no differences in mortality between patients who were severely burned receiving *rhGH* and those that did not.

All of our patient records were examined in detail by a pathologist and pediatrician, with no distinct pattern of pathologic findings being attributed to the use of *rhGH*. One patient developed hypoglycemia after cessation of *rhGH* in association with an increase in serum insulin levels that persisted into the period of hypoglycemia. Any patient receiving *rhGH* should be monitored closely for changes in serum glucose, similar to a patient on insulin therapy. Monitoring would be particularly important for continued *rhGH* therapy with abrupt cessation of diet, for example, as in before surgery. In this instance, intravenous glucose should be administered. Two children died from pulmonary failure. Both had identifiable smoke inhalation injuries and varying degrees of pulmonary fibrosis at autopsy, which is a common component of the pathologic findings of this injury. However, because of the mitogenic properties of *rhGH*, the potential for *rhGH* induced aggravation of a pulmonary injury exists. In examining the patients treated with *rhGH* as a therapeutic salvage maneuver, four of the eight deaths expired within 4 days of admission. This trend could not be identified in the children in the randomized study receiving *rhGH* due to the small number of deaths occurring in this group.

No differences in organ failure were identified. An increase in the evidence of sepsis in the rhGH treatment group compared with their controls (34% *vs.* 13%, respectively) was felt to be the result of the selection process for using rhGH in the most severely ill patients who were infected at the time of admission. The possibility exists, however, that rhGH treatment contributes to a higher incidence of the signs of sepsis directly or via the resultant hyperglycemia it causes.

We examined several physiologic and biochemical variables that could be associated with decompensation and death. We previously found an increase in serum glucagon and catecholamines with *rhGH* therapy after burn[18,19] an increase that was above that which is consequent to the trauma itself. The physiologic effects likely to be affected by such increases include chronotropic and inotropic hemodynamic effects and increased lipolysis.[20–22] We could find no differences between saline and *rhGH* treated groups in terms of heart rate or cardiac work, presumably because catecholamine stimulation was already maximal in the pediatric patients with massive burns. Barry et al.[23] demonstrated increased intraoperative cardiac indices by 50% in

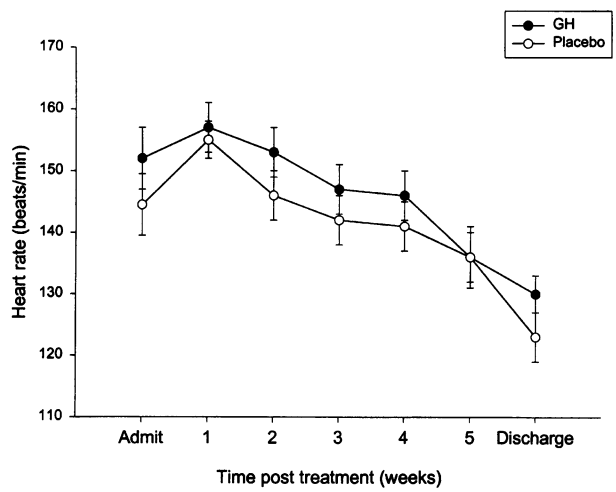

Figure 2. Schematic representation of changes in Heart Rate over hospital course in randomized study patients receiving either growth hormone (GH) or placebo. Data presented as means, bars are ±SEM.

patients receiving perioperative *rhGH* (0.3 IU/kg/day for 6 days pre- and/or postsurgery). The use of *rhGH* in certain patient subpopulations (*i.e.*, advanced or prolonged critical states, particular comorbid illnesses, and possibly age or organ function related issues), may contribute to rather than attenuate cardiac morbidity by stimulating an already hyperdynamic cardiac response. We believe that concomitant use of β-adrenergic blocking agents with *rhGH* may be necessary to prevent pathologic tachycardia if observed during treatment. We previously have found an increase in lipolysis in this population with *rhGH*.[24] The effect of this response might be an increase in hepatic fat deposition leading to diminished liver function. Propranolol treatment also would mitigate this response.[25]

In addition, we have shown that *rhGH* decreases glucose uptake and inhibits glucose oxidation in patients who are burned compared with saline controls. The diminished uptake and oxidation were roughly equivalent, indicating a deficiency in glucose transport.[26] Growth hormone is known to have diabetogenic effects, likely through these mechanisms. We have corroborated these conclusions in this study.

The most prominent physiologic effect in this patient population was an elevated serum glucose, which can be adequately treated with insulin therapy. However, it is probable that prolonged periods of hyperglycemia are present which are not detected and treated. Hyperglycemia can increase infectious risk by inhibiting white blood cell function and decreasing bacterial clearance, an effect found primarily in patients with diabetes with primary deficits in glucose metabolism.[27,28] Treatment with *rhGH* could amplify this impairment of the immune response. Further, the increased requirement for exogenous insulin therapy increases the potential for iatrogenic problems. On the positive side, we have shown that insulin therapy has beneficial effects on muscle anabolism[29] and wound healing in patients who are severely burned.[30] Therefore, the increase in insulin requirements among rhGH-treated children may be advantageous.

In this study, albumin was administered to restore normal serum concentrations with the goal of maintaining colloid osmotic pressure. We previously have shown that *rhGH* administration increased albumin gene expression and serum concentrations in burned rats.[31] In this study, albumin requirements were decreased by 65% in randomized study patients receiving *rhGH* compared with placebo, which corroborates these findings indicating a salutary effect of *rhGH* on albumin synthesis by the liver in burned children. The incidence of hypocalcemia was significantly lower in the *rhGH* treated group compared with placebo treated patients, perhaps through its known stimulation of osteoblast activity.

We have previously shown that catabolic hormones such as catecholamines, glucagon, and cortisol increased with *rhGH* treatment.[32] These increases could lead to deleterious side effects in some patients. We also have shown that *rhGH* further induces insulin resistance over that which is generally present in these patients.[33] The development of hyperglycemia was evident in these patients, however, this was not clinically troublesome. Upon review of all our patients that have received *rhGH* compared with their saline controls, we could find no differences in mortality, organ failure, or clinically significant morbidity. A 65% reduction in albumin supplementation requirements and reduced episodes of hypocalcemia were unexpected benefits. Treatment of severely burned children with *rhGH* can be achieved safely and without significant adverse side effects.

References

1. Pointing GA, Halliday D, Teale JD, et al. Postoperative nitrogen balance with intravenous hyponutrition and growth hormone. Lancet 1988;1: 438–439.
2. Byme TA, Morrissey TB, Gatzen C, et al. Anabolic therapy with growth hormone accelerates protein gain in surgical patients requiring nutritional rehabilitation. Ann Surg 1993;218: 400–418.
3. Petersen SR, Holaday NJ, Jeevanandam M. Enhancement of protein synthesis efficiency in parenterally fed trauma victims by adjuvant recombinant human growth hormone. J Trauma 1994;36: 726–733.
4. Douglas RG, Humberstone DA, Haystead A, Shaw JH. Metabolic effects of recombinant human growth hormone: isotopic studies in the postabsorptive state and during total parenteral nutrition. Br J Surg 1990;77: 785–790.
5. Voerman HJ, van Schijndel RJMS, Groenveld ABJ, et al. Effects of recombinant human growth hormone in patients with severe sepsis. Ann Surg 1992;216: 648–655.
6. Knox J, Demling R, Wilmore D, et al. Increased survival after major thermal injury: the effect of growth hormone therapy in adults. J Trauma 1995;39: 526–532.
7. Herndon DN, Barrow RE, Kunkel KR, et al. Effects of recombinant human growth hormone on donor site healing in severely burned children. Ann Surg 1990;212:424–431.
8. Gilpin DA, Barrow RE, Rutan RL, et al. Recombinant human growth hormone accelerates wound healing in children with large cutaneous burns. Ann Surg 1994;220: 19–24.
9. Herndon DN, Hawkins HK, Nguyen TT, et al. Characterization of growth hormone enhanced donor site healing in patients with large cutaneous burns. Ann Surg 1995;221: 649–659.
10. Herndon DN, Barrow RE, Kunkel KR, et al. Effects of recombinant human growth hormone on donor-site healing in severely burned children. Ann Surg 1990;211: 424–431.
11. Gilpin DA, Herndon DN, Rutan RL, et al. Recombinant human growth hormone accelerates wound healing in children with large cutaneous burns. Ann Surg 1994;220: 19–24.
12. Gore DC, Honeycutt D, Jahoor F, et al. Effect of exogenous growth hormone on whole-body and isolated limb protein kinetics in burned patients. Arch Surg 1991;126: 38–43.
13. Fleming RY, Rutan RL, Jahoor F, et al. Effect of recombinant human growth hormone on catabolic hormones and free fatty acids following thermal injury. J Trauma 1992;32: 608–702.
14. Public Communications from Pharmacia & Upjohn Pharmaceuticals and Rolf Gunnarsson, MD to all industry and medical community involved with the use or potential use of recombinant human growth hormone, Oct. 31, 1997.
15. Hildreth MA, Herndon DN, Desai MH, Duke MA. Caloric needs of adolescent patients with burns. J Burn Care Rehabil 1989;10: 523–526.
16. Hildreth MA, Herndon DN, Desai MH, Broemeling LD. Current treatment reduces calories required to maintain weight in pediatric patients with burns. J Burn Care Rehabil 1990;11: 405–409.

17. Wolf SE, Rose JK, Desai M, et al. Mortality determinants in massive pediatric burns: an analysis of 103 children with ≥80% TBSA burns (≥70% full-thickness). Ann Surg 1997;225: 554–569.
18. Fleming RY, Rutan RL, Jahoor F, et al. Effect of recombinant human growth hormone on catabolic hormones and free fatty acids following thermal injury. J Trauma 1992;32: 608–702.
19. Aarsland A, Chinkes D, Wolfe RR, et al. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone. Rate of hepatic very low density lipoprotein triglyceride secretion remains unchanged. Ann Surg 1996;223: 777–789.
20. Gobel FL, Nordstrom LA, Nelson RR. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 1978;57: 549–556.
21. Baller D, Bretschneider HJ, Hellige G. Validity of myocardial oxygen consumption parameters. Clin Cardiol 1979;2: 317–327.
22. Rooke GA, Feigl EO. Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. Circ Res 1982;50:273–286.
23. Barry MC, Mealy K, Sheehan S, et al. Cardio-respiratory function following elective aortic surgery: the effects of perioperative recombinant human growth hormone. Presentation at the 4th International Congress on the Immune Consequences of Trauma, Shock and Sepsis—Mechanisms and Therapeutic Approaches; 1997 Mar 4–8; Munich, Germany.
24. Aarsland A, Chinkes DL, Wolfe RR, et al. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone: rate of hepatic VLDL triglyceride secretions remains unchanged. Ann Surg 1996;23(6): 777–789. Ann Surg 1996;223: 777–789.
25. Aarsland A, Chinkes DL, Wolfe RR, et al. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone: rate of hepatic VLDL triglyceride secretions remains unchanged. Ann Surg 1996;23(6): 777–789.
26. Gore DC, Honeycutt D, Jahoor F, et al. Effect of exogenous growth hormone on glucose utilization in burn patients. J Surg Res 1991;51: 518–523.
27. McMahon MM, Bistrtrian BR. Host defenses ans susceptibility to infection in patients with diabetes mellitus. Infect Dis Clin North Am 1995;9(1): 1–9.
28. Eliashiv A, Olumide F, Norton L, et al. Depression of cell-mediated immunity in diabetes. Arch Surg 1978;113(10): 1180–1183.
29. Sakurai Y, Aarsland A, Herndon DN, et al. Stimulation of muscle protein synthesis by long-term insulin infusion in severely burned patients. Ann Surg 1995;222: 283–297.
30. Pierre EJ, Barrow RE, Hawkins HK, et al. Effects of insulin on wound healing. J Trauma 1998;44(2): 342–345.
31. Jarrar D, Wolf SE, Jeschke M, et al. Growth Hormone Attenuates the Acute Phase Response to Thermal Injury. Arch Surg 1997;132:1171–1176.
32. Fleming RY, Rutan RL, Jahoor F, et al. Effect of recombinant human growth hormone on catabolic hormones and free fatty acids following thermal injury. J Trauma 1992;32: 608–702.
33. Gore DC, Honeycutt D, Jahoor F, et al. Effect of exogenous growth hormone on glucose utilization in burn patients. J Surg Res 1991;51: 518–523.

Discussion

Dr. Douglas W. Wilmore (Boston, Massachusetts): We heard this morning when the Medallion for Scientific Achievement was awarded the great contributions that Dr. Pruitt and individuals working at the Burn Unit in San Antonio have made for the reduction in morbidity and mortality in burn patients. This afternoon an outstanding paper was presented that shows a mortality rate of only 2% in a group of burned children with an average burn size of 60% total body surface injury. This confirms the tremendous translation of research that moves to the clinic from the laboratory. This group and others have shown improvement in wound healing, pulmonary mechanics, and muscle strength with the administration of growth hormone. A large series now reported from Europe has shown a decrease in length of stay and an improvement in convalescence in individuals receiving growth hormone following total hip replacement. And another large series from Italy has shown that growth hormone can reduce congestive heart failure in patients receiving the drug. The question that has surprised us all with additional data from Europe demonstrating increased mortality in critically ill patients receiving growth hormone: Is this selection of patients? Or is it individual physician or hospital effect? We heard this morning that physicians who have greater experience with an operation actually do a better job. And this same experience factor apply with the use of more complex and complicated drugs? In this regard, I would like to ask the authors: Is there data available from this series of increased production of cytokines or other pro-oxidants as a result of giving growth hormone? Growth hormone can in fact stimulate free radical production. Do you have evidence at all that that may be occurring in this group of patients? Is there any data available from your patient groups as to those who have responses with IGF-1 production? We demonstrated that those critically injured patients who could not increase serum concentrations of IGF-1 would in fact have a higher mortality rate than those who could. Is that data present in your data set? Finally, is there an increased mobilization of free fatty acids that occurs when growth hormone is administered to these patients? Fatty acids are deleterious to some cells, and indeed in these severe catabolic situations may affect cardiac function. We have learned from the European study that a very expensive and very potent drug may have toxic effects. But we have heard this afternoon that if used cautiously and correctly with appropriate guidelines, it may have real benefits to our patients. I think it throws up a flag of caution that certainly should encourage us all to proceed carefully and cautiously so we can reduce convalescence in many of our critically ill patients with the safe use of growth factors. Thank you.

Dr. David N. Herndon (Galveston, Texas): In answer to your specific questions, we have shown a decrease in Interleukin-6 production with recombinant human growth hormone in the same patient population. We have not seen increase in other cytokines. We have not seen an increase in other cytokines. We have not yet looked at antioxidant production; however, vitamin E levels are massively decreased in all of these patients. We have not seen differences between them, but are going to investigate just that. IGF-1 production is increased threefold in these patients. We were not able to see differences in IGF-1 levels in those that died versus those that lived. There is a marked increase in mobilization of free fatty acids caused by growth hormone. There is also an increase in cardiac work. In the future, the modulation of that response in certain patient groups by beta blocking agents such as propranolol might be indicated.

Dr. Basil A. Pruitt, Jr. (San Antonio, Texas): I rise to join Dr. Wilmore in complimenting Dr. Ramirez and Dr. Herndon on this impressive body of work. To help us evaluate their conclusions, we need some additional information. Dr. Herndon, you note that in the salvage group, that is those admitted 8 days postburn some of whom had infection, there was a lesser need for albumen supplementation. How do you account for that apparent paradox? Did the excess or deficit in calcium and phosphate relate to the time postburn? That is, were calcium and phosphorus high early postburn at the time of tissue destruction and low later when the lean body mass was being reconstituted? Since IGF-1 increases phosphate reabsorption by the proximal tubule, did the phosphorus levels correlate with IGF-1 levels?