

Oxandrolone Treatment in Adults with Severe Thermal Injury

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Severe thermal injury is associated with hypermetabolism and hypercatabolism, leading to skeletal muscle breakdown, lean body mass loss, weight loss, and negative nitrogen balance. Muscle protein catabolism in patients with severe thermal injury is the result of stress-induced increased release of cytokines and counterregulatory hormones. Coupled with decreased serum anabolic hormone concentrations such as testosterone and growth hormone along with the presence of insulin resistance, anabolism in patients with severe thermal injury is inefficient or impossible during the acute postburn period. This causes difficulty in restoring lean body mass and regaining lost body weight, as well as poor healing of the burn wound and delayed patient recovery. Oxandrolone, a synthetic derivative of testosterone, has been used in adult patients with severe thermal injury to enhance lean body mass accretion, restore body weight, and accelerate wound healing. In clinical studies, oxandrolone 10 mg orally twice/day improved wound healing, restored lean body mass, and accelerated body weight gain. During the rehabilitation period, oxandrolone therapy with adequate nutrition and exercise improved lean body mass, increased muscle strength, and restored body weight. However, most data on oxandrolone use in adult patients with severe thermal injury are derived from single-center studies, many of which enrolled a relatively small number of subjects and some of which had a poor design. Multicenter, prospective, randomized studies are needed to better define the optimal oxandrolone dosage and to confirm the efficacy and safety of this drug in adult patients with severe thermal injury.

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OUTLINE

Metabolic Changes

Nutrition Support

Anabolic Hormone Therapy

Recombinant Human Growth Hormone

Recombinant Human Insulin-Like Growth Factor-1

Insulin

Testosterone

Oxandrolone

Clinical Studies of Oxandrolone

Acute Postburn Period

Rehabilitation Period

Summary of Efficacy

Safety

Cost

Conclusion

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Severe thermal injury is associated with metabolic and hormonal changes that correlate with the extent and severity of injury. During the period immediately after the severe thermal

injury, hypermetabolism and hypercatabolism result in skeletal muscle breakdown and loss of lean body mass. Anabolic agents including recombinant human growth hormone, recombinant human insulin growth factor-1 (IGF-1), insulin, testosterone, and oxandrolone have been used to enhance lean body mass accretion, promote wound healing, and restore body weight of patients with severe thermal injury.¹

Metabolic Changes

The metabolic response to severe thermal injury is biphasic. The early “ebb” phase occurs immediately after the injury and is characterized by hypovolemia, tissue hypoxia, and decreased cardiac output, oxygen consumption, body temperature, and metabolic rate. The subsequent 12–24 hours is the “flow” phase, which is characterized by increased cardiac output and oxygen consumption, hypermetabolism, and hypercatabolism.² During the flow phase, increased release of counterregulatory hormones (catecholamines, glucocorticoids, glucagon) and cytokines (interleukin-1, interleukin-6, tumor necrosis factor- α) cause proteolysis, lipolysis, and glycogenolysis.³ Patients with total body surface area (TBSA) burns of 60% or greater are at higher risk for morbidity and mortality compared with those with smaller TBSA burns. This may likely be due to increased hypermetabolic and inflammatory reactions as well as impaired cardiac function with larger thermal injuries. Protein breakdown correlates with the percent TBSA burn and the patient’s metabolic rate.⁴ Sepsis and hyperglycemia further aggravate catabolism. Protein catabolism results in lean body mass loss and negative nitrogen balance. Urinary and wound nitrogen losses are significantly increased such that protein synthesis is unable to compensate for nitrogen breakdown. Amino acid metabolism is also disrupted, with decreased amino acid influx into cells relative to increased amino acid efflux.⁵ Stress-induced hyperglycemia and insulin resistance are common in critically ill patients with severe thermal injury. Uncontrolled hyperglycemia increases proteolysis by 3-fold and is associated with higher frequency of graft failure and infections.^{3, 6} Lipid metabolism is also altered, with accelerated lipolysis resulting in free fatty acid release at a rate that exceeds fatty acid oxidation, which leads to hypertriglyceridemia.⁷ Diminished fat utilization limits the lipid protein-sparing effect whereby muscle proteins become a

preferential source of energy.⁸ Bone demineralization that is mediated by increased endogenous corticosteroid and cytokine production also occurs and may result in skeletal growth delay in children with severe thermal injury.⁹

Decreased serum endogenous anabolic hormone production during severe thermal injury further delays muscle mass and body weight gain and wound healing. Significant weight loss up to approximately 22% of preburn weight can occur by 8 weeks after severe thermal injury in patients with more than 40% TBSA burn.¹⁰ Despite adequate nutrition, patients with severe thermal injury may stay in negative nitrogen balance for months after the thermal injury.

Nutrition Support

The hypermetabolic response to severe thermal injury is characterized by a shift in blood supply to provide energy and nutrients to thermal injury wounds. Sympathetic hyperactivity causes tachycardia and increases myocardial contractility, cardiac workload, oxygen consumption, and metabolic rate.¹¹ Because metabolic rate varies among patients with severe thermal injury, indirect calorimetry using serial resting energy expenditure (REE) measurements is the most accurate method to measure energy expenditure, rather than relying on the less accurate energy predictive equations. The REE correlates with thermal injury size, presence of sepsis, ventilator dependence, and protein catabolism. In pediatric patients with greater than 40% TBSA burn, REE reached 180% of the basal metabolic rate during the acute postburn period, then decreased incrementally to 150% by the time of full wound healing around 2 months after the thermal injury, but remained at 115% at 12 months after thermal injury.¹² Interventions used to decrease the metabolic rate would reduce energy expenditure. These include proper sedation, control of pain and anxiety, maintenance of ambient patient room temperature at 30–32°C, early wound grafting and excision, prompt treatment of infections, supportive psychotherapy, and propranolol therapy to modulate the hypermetabolic response.¹³ Propranolol is used in patients with severe thermal injury to block β -adrenergic stimulation to decrease hypermetabolism and reduce muscle protein catabolism.¹⁴

Providing adequate nutrition to patients with severe thermal injury is essential to prevent malnutrition, attempt to achieve anabolism, maintain adequate immune system, and enhance

burn wound repair. Wound healing is a complex process of cellular, molecular, and biochemical aspects that directly correlates with the nutritional status. Malnutrition impairs wound healing, whereas providing adequate nutrition modulates the wound healing process.¹⁵ Nutrition support should provide daily calories at the level of measured REE. Increasing caloric intake beyond 1.2 times the REE does not improve lean body mass, but increases body fat deposition.¹⁶ Balancing caloric intake should be guided by macronutrient utilization and tolerance. Overfeeding should be avoided because it leads to serious metabolic complications including hyperglycemia, hypertriglyceridemia, cholestasis, hepatic steatosis, and respiratory compromise.^{17, 18} Adequate protein intake allows lean body mass building and promotes wound healing. In adult patients with severe thermal injury whose kidney and liver functions are normal, amino acids are provided at 1.5–2 g/kg/day. For optimal glucose oxidation and metabolism, continuous dextrose infusion rates should not exceed 4–5 mg/kg/minute in adult patients receiving parenteral nutrition.^{17, 19}

Enteral feeding is the preferred route of nutrition support in critically ill patients with severe thermal injury who have a functional gastrointestinal tract. Enteral nutrition preserves intestinal integrity and immunity, and is associated with less infectious and metabolic complications compared with parenteral nutrition.²⁰ Parenteral nutrition is indicated only when enteral nutrition cannot or should not be used such as in patients with adynamic ileus or intestinal obstruction. Using supplemental parenteral nutrition to enteral feeding has no clinical benefits and may increase patient mortality.²¹ Although some studies report that early (≤ 24 hrs of injury) enteral nutrition may blunt the hypermetabolic response of thermal injury, a systematic review of randomized controlled studies found no conclusive evidence that this practice reduces patient mortality or shortens the length of hospital stay.²² The role of enteral immune-enhancing nutrients (glutamine, arginine, omega-3 fatty acids) on the outcome of patients with severe thermal injury is controversial, and the use of immune-enhancing formulas varies among burn units.^{23, 24} Zinc, copper, selenium, and vitamins C, E, and A play a role in wound healing and reepithelialization.¹⁵ Supplementation of these micronutrients to the nutrition regimen of patients with thermal injury is common practice, although their exact requirements and evidence supporting their use are unclear.²⁵

Anabolic Hormone Therapy

Serum anabolic hormone concentrations are decreased after severe thermal injury, which negatively affects anabolism and wound healing. Anabolic agents including recombinant human growth hormone, recombinant human IGF-1, insulin, testosterone, and oxandrolone have been used in patients with severe thermal injury as adjunct therapies to proper wound care, nutrition support, and exercise programs during postburn rehabilitation in order to promote anabolism, protein synthesis, and wound healing; restore body weight; and improve physical functionality. However, these pharmacologic agents can be associated with adverse events that limit their clinical use.²⁶

Recombinant Human Growth Hormone

Recombinant human growth hormone increases cellular uptake of amino acids, enhances protein synthesis, and improves wound healing by binding to growth hormone receptors or increasing IGF-1 release.²⁶ In pediatric patients with severe thermal injury, recombinant human growth hormone improved wound healing, bone mineralization, and growth.²⁷ Recombinant human growth hormone use in critically ill patients is limited because it may cause hyperglycemia, hypertriglyceridemia, and fluid retention, and increases metabolic rate.^{26, 27} Recombinant human growth hormone has been safely used in critically ill patients with thermal injury.^{27–29} However, two prospective, multicenter, double-blind, randomized, placebo-controlled studies of critically ill adult patients without burn injury showed that administration of subcutaneous recombinant human growth hormone 0.1 mg/kg once/day for up to 21 days was associated with increased morbidity and mortality.³⁰ Deaths were attributed to multiorgan failure, septic shock, or uncontrolled infection. Although patients with thermal injury were excluded from the study, the study's negative results called into question the safety of growth hormone use in critically ill patients.

Recombinant Human Insulin-Like Growth Factor-1

The hormone IGF-1 (somatomedin-C) is a polypeptide hormone that mediates the effects of growth hormone. Recombinant human IGF-1 infusion in patients with severe thermal injury increases protein synthesis and reduces hyper-

metabolism. The effects of recombinant human IGF-1 on wound healing are unclear. It is associated with hypoglycemia and requires continuous infusion that limits its clinical use.²⁶ Intravenous infusion of a recombinant compound of IGF-1 with its binding protein-3 (IGFBP-3) significantly improved muscle protein synthesis in hypercatabolic patients with thermal injury; however, the outcomes of IGF-1-IGFBP-3 infusion were not superior to those observed with insulin or testosterone alone, and the IGF-1-IGFBP-3 cost outweighs its clinical benefits.¹

Insulin

Insulin is a potent anabolic hormone that increases protein synthesis and may improve wound healing by increasing availability of proteins for burn wounds.³¹ Because endogenous insulin effects are hampered by insulin resistance, exogenous insulin infusion is beneficial in decreasing muscle protein loss by stimulating protein synthesis and controlling hyperglycemia.³²⁻³⁴ Continuous insulin infusion suppresses hepatic glucose production, enhances peripheral glucose uptake, increases net protein synthesis, increases lean body mass, and accelerates skin donor site healing in patients with severe thermal injury.³⁵⁻³⁷ Maintaining normoglycemia (blood glucose concentrations 80–110 mg/dl) in surgical critical care adult patients with use of intensive continuous-infusion insulin significantly decreased patient morbidity and mortality.³⁸ However, intensive insulin therapy is associated with hypoglycemia and requires continuous infusion with around-the-clock blood glucose monitoring. Severe hypoglycemia (blood glucose concentrations < 40 mg/dl) is a risk factor for increased patient morbidity and mortality.^{32, 38, 39}

Testosterone

Testosterone binds to androgenic receptors and increases cellular amino acid uptake and protein synthesis. Testosterone may also improve wound closure and reepithelialization, and stimulate collagen synthesis and deposition in wounds.²⁶ Testosterone enanthate 200 mg/week intramuscular injection was associated with a 2-fold increase in protein synthetic rate and significant reduction in muscle protein breakdown.⁴⁰ However, testosterone use in patients with severe thermal injury has been limited because of its androgenic effects and potentially serious liver toxicity.⁴¹

Oxandrolone

Oxandrolone is a synthetic 17 α -methyl derivative of testosterone but with a more favorable pharmacologic profile. Oxandrolone has 10 times more anabolic effects and only 10% of the adverse androgenic effects of testosterone. Because of its improved safety profile and ease of oral administration, oxandrolone is most commonly used for its anabolic effects in patients with severe thermal injury.⁴⁰ In skeletal muscles, oxandrolone binds to intracellular androgen receptors. The androgen receptor-oxandrolone complex then migrates to the cell nucleus where it binds to DNA and stimulates protein synthesis and anabolism. Oxandrolone also exhibits its anabolic effects by countering the catabolic effects of cortisol through competitive inhibition of the glucocorticoid receptor.⁴² Protein kinetic studies showed oxandrolone to increase intracellular amino acid influx and utilization, and improve the efficiency of skeletal muscle protein synthesis. This effect may possibly be mediated by an oxandrolone-induced increase of the androgen receptor expression in skeletal muscles. Oxandrolone, however, has no effect on intracellular protein transport or protein break-down. A DNA array analysis also showed that oxandrolone alters the expression of 21 genes and decreases the expression of transcription factors and signaling molecules that are believed to correlate with oxandrolone effects on ameliorating the inflammatory response of severe thermal injury.^{43, 44} Further, oxandrolone effects on wound repair may be mediated by stimulation of procollagen messenger RNA expression in fibroblasts, thereby increasing collagen synthesis and deposition in the healing wound.⁴⁵

Oxandrolone is well absorbed after oral administration and is highly bound (94–97%) to plasma proteins. In healthy volunteers, the elimination half-life of oxandrolone in young individuals is 10.4 hours but increases in the elderly to 13.3 hours. Time to peak concentration, peak plasma concentration, and bioavailability do not differ with age.⁴⁶ Unlike other anabolic steroids, oxandrolone is not as extensively metabolized by the liver. About 28% of the oral oxandrolone dose is excreted unchanged in the urine and about 3% is eliminated in the feces.⁴⁷ Although no specific recommendations for dosage adjustments have been published for patients with decreased renal function, caution should be used in patients with renal insuffi-

ciency because oxandrolone can induce edema and heart failure in patients with preexisting renal, cardiac, or liver disease.⁴⁶ Sodium and water retention with exacerbation of hypertension and deterioration of kidney function were reported with oxandrolone 20 mg/day in patients with severe renal insufficiency and hypertension.⁴⁸

Oxandrolone is labeled by the United States Food and Drug Administration for use as adjunct therapy to restore body weight after extensive surgery, chronic infections, and severe trauma; to offset protein catabolism associated with chronic corticosteroid use; and to relieve osteoporotic bone pain. Oxandrolone therapy can be associated with serious adverse effects, but the frequency of these adverse effects is unknown. Oxandrolone-induced adverse effects may include hepatotoxicity (increased hepatic transaminase concentrations, hyperbilirubinemia, cholestatic jaundice, hepatic failure), delayed bone growth and premature closure of epiphyses in children, sexual changes (clitoral enlargement, menstrual irregularities), virilization (hirsutism, vocal cord growth), genitourinary effects (priapism, testicular atrophy, bladder irritation) mainly in prepubertal male patients, hyperglycemia, hyperlipidemia, electrolyte disturbances, and central nervous system disturbances (depression, excitation, insomnia). The oxandrolone package insert includes a black-box warning for peliosis hepatitis, liver cell malignant tumors, and dyslipidemia, as reported with androgens and anabolic steroids. Contraindications to oxandrolone include androgenic-sensitive tumors, pregnancy, nephrosis, and hypercalcemia.⁴⁶

In pediatric patients with severe thermal injury, oxandrolone 0.1 mg/kg twice/day in the acute postburn period improved serum visceral protein concentrations, increased lean body mass accretion, improved muscle strength, promoted weight gain, and increased bone mineral content. Also, during rehabilitation of pediatric patients after thermal injury, oxandrolone 0.1 mg/kg/day improved lean body mass, muscle strength, and cardiopulmonary capacity in combination with adequate nutrition and physical therapy.⁴⁹⁻⁵³ Oxandrolone 10 mg twice/day has been shown to improve wound healing, restore lean body mass, and promote weight gain in adults with severe thermal injury.⁵⁴⁻⁶¹

Clinical Studies of Oxandrolone

Table 1 summarizes the clinical studies of oxan-

drolone in adults with severe thermal injury, including use of oxandrolone in the acute postburn period⁵⁴⁻⁵⁸ and in the rehabilitation period.⁵⁹⁻⁶¹

Acute Postburn Period

A prospective, randomized, double-blind, placebo-controlled study evaluated the effects of oxandrolone in the acute postburn period in 20 adult patients with severe thermal injury.⁵⁴ Beginning 2-3 days after thermal injury, patients were randomly assigned to receive oxandrolone 10 mg twice/day (11 patients) or placebo (9 patients). Despite similar caloric and protein intake between the two groups, oxandrolone-treated patients had significantly less weight loss (mean \pm SD 3 \pm 1.9 vs 8 \pm 3 kg, $p < 0.05$) and nitrogen loss (4 \pm 1.9 vs 13 \pm 4 g/day, $p < 0.05$) over 3 weeks compared with placebo. Oxandrolone caused significantly faster wound healing compared with placebo (9 \pm 2 vs 13 \pm 3 days, $p < 0.05$). Mild asymptomatic elevation of liver function tests (magnitude not reported) occurred in 50% and 57% of patients in the oxandrolone and control groups, respectively, but differences were not statistically significant. Mean \pm SD burn unit length of stay for patients in the oxandrolone and placebo groups was 29 \pm 8 and 35 \pm 9 days, respectively. However, the small study sample was insufficient to draw a valid comparison for the length of stay.

A large multicenter, prospective, randomized, double-blind, placebo-controlled study further evaluated the effects of oxandrolone on the length of stay in the acute postburn period in 81 adult patients.⁵⁵ Patients were randomly assigned to receive oxandrolone 10 mg twice/day (46 patients) or placebo (35 patients) beginning on day 5 after thermal injury and continued until hospital discharge. Study results showed oxandrolone to be associated with a 27% shorter length of hospital stay, which was significantly shorter in oxandrolone-treated patients compared with control (mean \pm SD 31.6 \pm 3.1 vs 43.3 \pm 5.3 days, $p = 0.042$). When patient mortality was excluded, the length of stay remained significantly shorter in the oxandrolone group compared with placebo (32 \pm 3.1 vs 45.3 \pm 5.4 days, $p = 0.035$). Results were also consistent when adjusted for percent TBSA burn and patient mortality was excluded (mean \pm SD 0.88 \pm 0.07 vs 1.23 \pm 0.15 days/%TBSA, $p = 0.015$). Further, oxandrolone-treated patients underwent significantly fewer surgeries compared with patients in the placebo group (2.2 \pm 0.3 vs 4 \pm 0.6

Table 1. Clinical Studies of Oxandrolone in Adult Patients with Severe Thermal Injury

Study Design	Patient Population	Nutrition Support	Duration of Oxandrolone Therapy ^a	Primary Outcomes
Acute postburn period				
Prospective, randomized, double-blind, placebo-controlled (n=20) ⁵⁴	Oxandrolone (n=11) Placebo (n=9) 40–70% TBSA burn	Enteral, supplemental parenteral p.r.n. 32–34 kcal/kg Protein 1.6–1.7 g/kg	Mean ± SD of 33 ± 9 days until transfer to rehabilitation	Net weight loss, nitrogen loss, time to wound healing, metabolic rate, liver dysfunction, LOS
Prospective, multicenter, randomized, double-blind, placebo-controlled (n=81) ⁵⁵	Oxandrolone (n=46) Placebo (n=35) 20–60% TBSA burn	Enteral or oral nutrition (amounts not reported)	Started 5 days after thermal injury and continued until hospital discharge	LOS, hospital charges, ventilator days, discharge disposition
Prospective, randomized, controlled (n=22) ⁵⁶	Oxandrolone (n=11) Control (n=11) Mean ± SD % TBSA burn: 33 ± 9% in patients with thermal injury, 42 ± 15% in patients with skin slough disorders (TEN, GVHD)	Not reported	Started within 48 hrs of burn unit admission ^b ; duration not reported	Time to wound healing, weight loss, complications
Prospective, randomized, controlled (n=50) ⁵⁷	Elderly (mean age 70 yrs) Oxandrolone (n=26) Control (n=24) 10–29% TBSA burn	Not reported	Started on admission and continued until discharge	Weight loss, wound healing, nitrogen loss, LOS, infectious complications
Prospective, randomized, comparative (n=60) ⁵⁸	Adults with > 25% TBSA burn Oxandrolone (n=16) RhGH (n=20) Control (n=24) ^c Mean ± SD % TBSA burn: 56 ± 15% in both treatment groups, 52 ± 14% in control group	Enteral, supplemental parenteral p.r.n. Amino acids 2 g/kg/day	Started 7–10 days after thermal injury and continued until discharge to rehabilitation ^b	Wound healing, weight loss, nitrogen loss, metabolic rate, complications
Postburn rehabilitation period				
Prospective, randomized, controlled (n=23) ⁵⁹	Oxandrolone with high-protein diet (n=7) High-protein diet (n=6) Lower protein diet (n=10) 30–50% TBSA burn	Protein 2 g/kg/day in oxandrolone group and in high-protein diet group, 1.3–1.4 g/kg/day in lower protein diet group 30–35 kcal/kg/day	3 wks	Weight gain, muscle strength
Prospective, randomized, controlled (n=45) ⁶⁰	Oxandrolone (n=23) Control (n=22) Mean ± SD % TBSA burn: 40 ± 14% in oxandrolone group, 37 ± 15% in controls	33–34 kcal/kg/day Protein 1.4–1.6 g/kg/day	Started on admission to rehabilitation facility and continued until restoration of 90% of body weight ^b	Body weight, body composition

surgeries/patient, $p=0.015$). After 7 weeks of hospitalization, a significantly higher number of asymptomatic increases in serum alanine

aminotransferase concentration (ALT > 100 mg/dl) was noted in the oxandrolone group compared with placebo (21 vs 6, $p=0.002$). The

Table 1. (continued)

Results
Oxandrolone significantly decreased weight loss, nitrogen loss, and wound healing time; no significant differences in metabolic rate or hepatic effects; LOS could not be compared
Compared with placebo, oxandrolone decreased LOS (mean \pm SD 31.6 \pm 3.1 vs 43.3 \pm 5.3 days, $p=0.042$) and decreased LOS adjusted for mortality and for % TBSA burn; there were fewer surgeries/patient in oxandrolone group; the oxandrolone group had significantly more occurrences of ALT concentration elevations; no significant differences in ventilator days, discharge disposition, or hospital charges
Compared with control, oxandrolone, decreased time to wound healing (mean \pm SD 13 \pm 3 vs 20 \pm 4 days, $p<0.05$); oxandrolone reduced weight loss; no significant difference in complications
Oxandrolone reduced weight loss in the 10–19% and 20–29% TBSA burn subgroups; it decreased time to wound healing, nitrogen loss, and LOS adjusted for % TBSA burn; no significant difference in incidence of pneumonia
Compared with control, oxandrolone and RhGH decreased time to wound healing (mean \pm SD 14 \pm 2 vs 10 \pm 2 and 10 \pm 3 days, $p<0.05$), nitrogen loss (11 \pm 3.2 vs 3 \pm 1.5 and 4 \pm 2.4 g/day, $p<0.05$), and weight loss; RhGH increased metabolic rate vs control (mean \pm SD 72 \pm 11 vs 50 \pm 12%, $p<0.05$) and caused hyperglycemia; no significant differences between oxandrolone and RhGH groups for skin donor site healing time, weight loss, or nitrogen loss; no significant difference in percentage of patients who had increased liver function test results
Oxandrolone plus high-protein diet caused more significant absolute weekly weight gain vs high-protein diet alone (mean 1.7 vs 1.1 kg in week 1, 1.8 vs 1.1 kg in week 2, and 2.1 vs 1.1 kg in week 3, $p<0.05$); high-protein diet alone caused more significant weekly weight gain vs lower protein diet alone (mean 1.1 vs 0.5 kg in week 1, 1.1 vs 0.5 kg in week 2, and 1.1 vs 0.6 kg in week 3, $p<0.05$)
Oxandrolone increased muscle strength; body weight at weeks 1, 2, 3, and 4; and lean body mass at discharge and at 6 mo after discharge; no complications reported

difference in the number of increased serum aspartate aminotransferase concentrations (AST > 100 mg/dl) did not reach statistical significance

between the oxandrolone and placebo groups (11 vs 9, $p=0.738$). Because serum transaminase concentrations were reported at the discretion of investigators, a valid conclusion of oxandrolone effects on liver function tests cannot be drawn. The authors attribute the lack of generated cost savings despite decreased length of stay to possible inadequate study power to test for costs, or to the relatively higher costs earlier in the course of patient hospital stay, with hospital charges possibly linked to diagnosis-related groups and billing codes that do not account for the length of stay in the charges. The study was halted with approximately half of projected subjects enrolled because interim analysis showed significant difference in favor of oxandrolone compared with placebo.

Corticosteroids increase catabolism, blunt the inflammatory phase of wound healing, and reduce collagen deposition, which further impair wound healing.^{62, 63} A prospective, randomized, controlled study evaluated the effects of oxandrolone on wound healing in 22 adult patients with severe thermal injury (12 patients) or skin slough disorders (toxic epidermal necrolysis in seven patients, graft-versus-host disease in three) who were receiving high-dose corticosteroids for treatment of diseases necessitating steroid therapy (e.g., collagen vascular disease, solid-organ transplantation, bone marrow transplantation, asthma).⁵⁶ At baseline, patients with thermal injury were receiving a mean \pm SD hydrocortisone dose of 150 \pm 50 mg/day, and those with skin slough disorders 190 \pm 75 mg/day. Patients were randomly assigned to receive standard care, or standard care with oxandrolone 20 mg/day starting within 48 hours of admission to the burn unit. Patients treated with corticosteroids were also compared with a similar group of non-steroid-treated patients with thermal injury (15 patients) or toxic epidermal necrolysis (10 patients) who received the same standard care during the same time period. Patients treated with hydrocortisone and who received oxandrolone had significantly faster donor site wound healing (mean \pm SD 13 \pm 3 vs 20 \pm 4 days, $p<0.05$) and 43% less weight loss (4 \pm 2 vs 7 \pm 3 kg, $p<0.05$) compared with patients receiving standard care alone (control group). Similarly, patients with skin slough disorders treated with hydrocortisone and who received oxandrolone had significantly faster wound reepithelialization (mean \pm SD 17 \pm 4 vs 25 \pm 6 days, $p<0.05$) and 50% less weight loss (4 \pm 2 vs 8 \pm 3 kg, $p<0.05$) compared with

Table 1. Clinical Studies of Oxandrolone in Adult Patients with Severe Thermal Injury (continued)

Study Design	Patient Population	Nutrition Support	Duration of Oxandrolone Therapy ^a	Primary Outcomes
Postburn rehabilitation period (continued)				
Prospective, randomized, controlled, parallel-group (n=40) ⁶¹	Oxandrolone (n=21) Control (n=19) Mean \pm SD % TBSA burn by age: 47 \pm 10% (18–40 yrs) vs 36 \pm 5% (\geq 55 yrs), p<0.05	18–40-yr-old group: 31 \pm 5 kcal/kg/day Protein 1.6 g/kg/day \geq 55-yr-old group: 30 \pm 6 kcal/kg/day Protein 1.5 g/kg/day	4 wks or until recovery of preburn weight	Weight gain, lean body mass gain, functional independence

TBSA = total body surface area; LOS = length of stay; ALT = alanine aminotransferase; TEN = toxic epidermal necrolysis; GVHD = graft-versus-host disease; RhGH = recombinant human growth hormone.

^aUnless otherwise indicated, oxandrolone daily dose was 20 mg, administered as 10 mg twice/day.

^bThe oxandrolone dosage was reported at 20 mg/day, but whether it was given once/day or divided into two daily doses was not specified.

^cPatients with severe thermal injury (> 50% TBSA burn, or > 25% TBSA burn with impaired wound healing or comorbidities) who were not eligible for oxandrolone therapy.

the control group. Patients who received standard care alone but were treated with corticosteroids had longer donor site wound healing time compared with patients who did not receive corticosteroids (mean \pm SD 20 \pm 4 vs 12 \pm 3 days for burned patients, 25 \pm 6 vs 18 \pm 4 days for patients with skin slough disorders); however, these differences were not statistically significant. Mild, transient elevations of serum AST and ALT concentrations were reported in five patients in the oxandrolone group and in seven patients in the standard-care group. Increases in serum transaminase concentrations were deemed related to stress effects on the liver rather than to oxandrolone. No hirsutism was reported in the 11 women who received oxandrolone for 3–4 weeks. Oxandrolone had no effect on infection rates. Although oxandrolone enhanced wound healing even during corticosteroid therapy, it is unclear whether this effect was due to counteracting the catabolic and antiinflammatory effects of corticosteroids. It is counterproductive if oxandrolone blunts the antiinflammatory effects of corticosteroids.

Elderly patients with severe thermal injury are at increased risk for morbidity and mortality due to decreased immune function, higher susceptibility to infections, and high risk for cardiopulmonary failure.^{64, 65} With older age, decreased physical function, lean body mass, and endogenous anabolic hormone synthesis delay wound healing and recovery in elderly patients with severe thermal injury.⁶⁶ Fifty elderly

patients (mean age 70 yrs) with 10–29% TBSA burn were randomly assigned on admission to the burn unit to receive oxandrolone 10 mg twice/day plus standard thermal injury care or standard care alone (control group).⁵⁷ Patients were stratified by percent TBSA burn subgroups: 10–19% and 20–29%. The oxandrolone dosage was adjusted to once/day in patients with creatinine clearances that were less than 25% of normal for age. Oxandrolone was continued until discharge or transfer to a rehabilitation facility. Oxandrolone use was associated with significantly less body weight loss (as a percentage of total weight) compared with the control group in both the 10–19% TBSA burn subgroup (mean \pm SD 4 \pm 2% vs 9 \pm 2%, p<0.05) and the 20–29% TBSA burn subgroup (5 \pm 3% vs 9 \pm 2%, p<0.05). Time to donor site wound healing was significantly shorter in patients treated with oxandrolone compared with the control group in both the 10–19% TBSA burn subgroup (12 \pm 4 vs 16 \pm 5 days, p<0.05) and the 20–29% TBSA burn subgroup (12 \pm 5 vs 17 \pm 5 days, p<0.05). At all time periods, patients in the oxandrolone group had significantly less net nitrogen loss than the control group (p<0.05). Length of burn unit stay adjusted for percent TBSA burn was also significantly shorter in the oxandrolone group compared with control (p<0.05) and also compared with predicted national average length of stay for age and degree of thermal injury (p<0.05). Skin graft loss (defined as > 15% loss) as a surrogate marker of

Table 1. (continued)

Results
Oxandrolone increased mean weekly weight in younger and older patients by 1.7 and 1.6 kg, compared with 0.7 and 0.4 kg in the control group, respectively ($p < 0.05$); the drug increased lean body mass as percentage of total weight gain in younger (mean \pm SD $79 \pm 4\%$ vs $59 \pm 9\%$, $p < 0.05$) and older groups (mean \pm SD $76 \pm 5\%$ vs $51 \pm 6\%$, $p < 0.05$) vs control; it increased functional independence at weeks 3 and 4 in older patients; it also decreased LOS in both age groups

infection and wound healing was significantly less in the oxandrolone group compared with that in the control group. Pneumonia was diagnosed in 20% of the oxandrolone-treated patients and 30% of patients in the control group. Transient asymptomatic 2-fold increases in serum AST and ALT concentrations from baseline occurred in 20% of patients in the oxandrolone group (no drug discontinuation needed) and 25% of patients in the control group. To our knowledge, this is the first study of patients with severe thermal injury to reduce the oxandrolone dosage by 50% from 10 mg twice/day to 10 mg/day in patients with decreased renal function. However, the total daily dose of oxandrolone administered to patients with normal renal function was twice the maximum dosage of 5 mg twice/day recommended for geriatric patients.⁴⁶

Oxandrolone versus Recombinant Human Growth Hormone

A prospective, randomized, nonblinded study compared the anabolic effects of oxandrolone versus recombinant human growth hormone in the acute postburn period in 60 adult patients with severe thermal injury.⁵⁸ Patients were randomly assigned to receive oxandrolone 20 mg/day (16 patients) or intramuscular injection of human growth hormone 0.1 mg/kg/day (20 patients) beginning 7–10 days after thermal injury and having reached at least 85% of daily caloric and protein intake. Treatment continued until wound healing and recovery was sufficient to allow transfer to rehabilitation. Data were also compared with that of a control group of 24 patients with severe thermal injury in the burn unit who did not meet the study inclusion criteria for oxandrolone therapy. At baseline,

patients in the oxandrolone and human growth hormone groups had significantly greater percent TBSA burn and percent TBSA full-thickness thermal injury compared with the control group. Among patients with at least 25% TBSA burn with comorbid conditions, significantly more patients who received oxandrolone (seven patients) and human growth hormone (eight patients) had adult-onset diabetes mellitus compared with eight patients in the control group (72% and 80% vs 15%, $p < 0.05$). Study results showed that patients treated with oxandrolone and human growth hormone had significantly faster donor site healing than the control group (mean \pm SD 10 ± 2 and 10 ± 3 vs 14 ± 2 days, $p < 0.05$). Further, patients in the oxandrolone and human growth hormone groups had significantly less net weight loss during therapy than patients in the control group (mean \pm SD 3 ± 2 and 4 ± 2 vs 8 ± 3 kg, $p < 0.05$). Net daily nitrogen loss was significantly lower in the oxandrolone and human growth hormone groups compared with control. Patients treated with human growth hormone had a significant percent increase in their metabolic rate compared with control. All patients treated with human growth hormone developed hyperglycemia (serum glucose concentrations > 225 mg/dl) compared with 52% of patients in the oxandrolone group and 55% in the control group ($p < 0.05$). To maintain serum glucose concentrations below 225 mg/dl, greater than 60% of patients treated with human growth hormone required insulin therapy, compared with 28% and 25% of patients in the oxandrolone and control groups, respectively. A significantly higher percentage of patients treated with human growth hormone had underlying diabetes compared with the control group (80% vs 18%, $p < 0.05$), which may have further exacerbated hyperglycemia in the human growth hormone group. The percentages of patients who developed mild asymptomatic increases in serum AST, ALT, or alkaline phosphatase concentrations (increase by not more than 1.5 times normal) were similar in the oxandrolone, human growth hormone, and control groups. No hirsutism was reported in any of the groups. The length of burn unit stay was not compared because of significant baseline differences in thermal injury severity and comorbidities between the treatment and control groups. Although oxandrolone and human growth hormone showed similar beneficial effects on wound healing and nitrogen retention in adult patients with severe thermal injury, human

growth hormone was associated with a 2-fold increase in occurrence of hyperglycemia. Although historically hyperglycemia in critically ill patients was loosely defined as serum glucose concentrations exceeding 200 mg/dl, this high threshold is no longer acceptable. Intensive insulin therapy is a standard of practice to control hyperglycemia in critically ill patients and has been shown to decrease patient morbidity and mortality.^{38, 67} A study limitation is the baseline mismatch in percent TBSA burn between the treatment and control groups, and the control group supposedly consisted of excluded patients who did not meet the criteria for oxandrolone therapy.

Rehabilitation Period

The effects of oxandrolone on weight gain and muscle function were evaluated in a prospective, randomized, controlled study during rehabilitation of adult patients after thermal injury.⁵⁹ The treatment group (seven patients) received oxandrolone 10 mg twice/day with a high-protein 2-g/kg/day diet and was compared with two groups: an active control group of six patients with thermal injury who received a similar high-protein 2-g/kg/day diet but no study drug, and a retrospective group of 10 patients with severe thermal injury who consumed a lower protein 1.3–1.4-g/kg/day diet but no study drug. Patients included in the study were anticipated to require at least 3 weeks of rehabilitation, and they reached the recovery period within 4–6 weeks after thermal injury. Patients in all groups lost about 9 kg (12% of usual body weight) during their acute postburn period. Study results showed that during the recovery phase, overall average weight gain at the end of 3 weeks was significantly higher in the oxandrolone plus high-protein diet group compared with the high-protein and lower protein diets alone groups (mean \pm SD 6.6 \pm 1.1 vs 3.4 \pm 0.7 and 2 \pm 0.3 kg, $p < 0.05$). Muscle strength as assessed by physical therapy index (using cumulative endurance and strength exercise criteria ranking from lowest = 0 to highest = 10) was significantly higher at 3 weeks in the oxandrolone plus high-protein diet group compared with the high-protein diet and lower protein diet alone groups (8.8 \pm 0.5 vs 7 \pm 0.8 vs 4.1 \pm 0.5, $p < 0.05$); the difference in muscle strength between the high-protein diet alone and lower protein diet groups was also significant ($p < 0.05$). An asymptomatic transient increase of serum alkaline phosphatase concentration

(magnitude not reported) was reported in one patient in each of the oxandrolone and higher protein diet groups, but resolved spontaneously without oxandrolone discontinuation. No hirsutism, acne, or behavioral changes were reported. This study stressed the importance of high-protein intake at 2 g/kg/day on weight gain and muscle strength throughout rehabilitation of adults with severe thermal injury. A 1.7-fold increase in body weight gain during the 3-week rehabilitation program could be attributed to increasing protein intake alone from 1.4 to 2 g/kg/day. Further, a 2-fold body weight gain resulted from the addition of oxandrolone to the high-protein diet along with exercise. This study, however, did not address the effects of oxandrolone with high-protein intake and exercise on lean body mass changes.

The same investigators further evaluated the long-term effects of oxandrolone during and after rehabilitation of adults with severe thermal injury.⁶⁰ Forty-five adults with severe thermal injury who were anticipated to have at least 3 weeks of postburn rehabilitation were included in a prospective, randomized, controlled study. On admission to the rehabilitation facility, patients were randomly assigned to receive oxandrolone 20 mg/day in addition to adequate nutrition and exercise (23 patients) or to the control group where they received only adequate nutrition and exercise (22 patients). Oxandrolone was continued until restoration of at least 90% of lost weight. Body weight and body composition (bioelectric impedance analysis) were recorded at discharge from the rehabilitation facility, 6 months after discharge, and 6 months after oxandrolone discontinuation. Weight loss as a percentage of baseline body weight during the acute postburn period was similar in the oxandrolone and control groups (mean \pm SD 10 \pm 2% vs 9 \pm 2%, $p > 0.05$). Absolute weight gain was significantly higher in oxandrolone-treated patients compared with patients in the control group (1.8 vs 0.6 kg, 1.5 vs 0.7 kg, 1.5 vs. 0.7 kg, and 1.5 vs. 0.7 kg during weeks 1, 2, 3, and 4, respectively, $p < 0.05$). During rehabilitation, oxandrolone-treated patients regained body weight and lean body mass 2–3 times faster than patients receiving nutrition and exercise alone. At time of discharge from the rehabilitation facility, patients treated with oxandrolone had significantly more lean body mass (as percentage of total body weight) compared with patients who received nutrition and exercise alone (mean \pm SD 76 \pm 4% vs 71 \pm 3%, $p < 0.05$). The

difference was also sustained at 6 months after discharge. Of interest, less additional body weight gain from time of discharge to 6 months after discharge was reported in oxandrolone-treated patients compared with the control group, although the difference was not statistically significant (mean \pm SD 2.8 ± 1 vs 4.1 ± 1.2 kg, $p > 0.05$). Study results provide additional data of oxandrolone benefits on restoring lean body mass during rehabilitation and the rate of lean body mass regain extends for 6 months after oxandrolone discontinuation. This was achieved in combination with a rehabilitation exercise program and adequate nutrition.

A study of similar design by the same investigators randomly assigned 40 adult patients with severe thermal injury to receive oxandrolone 10 mg twice/day in addition to nutrition and exercise or nutrition and exercise alone during rehabilitation.⁶¹ Patients were stratified by age: the younger group included 25 patients aged 18–40 years (mean \pm SD 34 ± 5 yrs) and the older group included 15 patients aged 55 years or older (60 ± 5 yrs). Patients with prostate mass or history of prostate cancer were excluded from the study. Oxandrolone was started on admission to the rehabilitation facility and continued for 4 weeks or until patients recovered their preburn body weight. At baseline, younger patients had significantly larger percent TBSA burn, shorter burn unit stay, and shorter ventilator-dependence time, compared with older patients. Absolute weekly weight gain was significantly higher in younger patients treated with oxandrolone by weeks 2, 3, and 4 compared with patients in the nutrition and exercise group alone (1.7 vs 0.7 kg, 1.8 vs 0.7 kg, and 1.8 vs 0.8 kg, respectively, $p < 0.05$). Similarly, absolute weekly weight gain was significantly higher in older patients treated with oxandrolone compared with the nutrition and exercise group alone by weeks 1, 2, 3, and 4 (1.1 vs 0.3 kg, 1.6 vs 0.5 kg, 1.5 vs 0.5 kg, and 1.7 vs 0.6 kg, respectively, $p < 0.05$). Lean body mass accretion (using bioelectric impedance analysis) at week 4 of oxandrolone therapy was significantly higher in both younger and older groups compared with respective controls (mean \pm SD 7 ± 2.2 vs 3 ± 1.2 kg and 6 ± 1.9 vs 2 ± 0.9 kg, respectively, $p < 0.05$). Younger and older patients treated with oxandrolone also had lower fat mass as percentage of total body weight compared with controls, but these differences were not statistically significant. Measurement of musculoskeletal function was assessed by using the functional independence measurement (FIM)

scoring system that measures muscle endurance, strength, and function. On admission to the rehabilitation facility, all patients had significant impairment of their functional capacity with an absolute average FIM score of about 77 for the younger group (normal range 115–120) and 70 for the older group (normal range 105–110). Younger patients treated with oxandrolone had higher FIM scores by weeks 2, 3, and 4 compared with patients in the nutrition and exercise group alone (mean \pm SD 95 ± 8 vs 85 ± 7 , 105 ± 8 vs 88 ± 6 , and 107 ± 9 vs 90 ± 5 , respectively, $p < 0.05$). Older patients treated with oxandrolone achieved higher FIM scores only at weeks 3 and 4 compared with patients in the nutrition and exercise group alone (92 ± 5 vs 84 ± 8 and 96 ± 6 vs 86 ± 7 , respectively, $p < 0.05$). About 30% shorter length of rehabilitation time was reported in all patients treated with oxandrolone. Both younger and older patients treated with oxandrolone had significantly shorter rehabilitation stay compared with their respective controls (23 ± 6 vs 31 ± 5 days and 34 ± 5 vs 42 ± 5 days, respectively, $p < 0.05$). No patient treated with oxandrolone developed hirsutism or behavioral changes. Three patients treated with oxandrolone had a transient increase in alkaline phosphatase concentration not exceeding a 50% increase above normal, which resolved spontaneously without oxandrolone discontinuation. This was the only study, to our knowledge, that showed oxandrolone to significantly shorten the length of inpatient rehabilitation time in adults with severe thermal injury. The benefits of oxandrolone, in combination with an adequate nutrition and exercise program, were significant in increasing the rate of lean body mass restoration, promoting rapid regain of body weight, and rapidly restoring functional capacity in the rehabilitation of young and elderly patients with severe thermal injury. Further, older patients had significantly longer duration of dependence on mechanical ventilation and longer burn unit stay compared with the younger group. The study did not compare the outcomes of the younger with that of the older patient groups. A study limitation was that older patients received similar amounts of calories (average 35 kcal/kg/day) to that of younger patients, which would have provided relatively higher daily calories than required to older patients considering their lower body cell mass with aging. Excessive calorie intake from carbohydrates and fat would result in a significant increase in body fat weight rather than body cell mass weight.

Summary of Efficacy

Adjunct oxandrolone 10 mg twice/day in adult patients with severe thermal injury improves burn wound healing, restores lean body mass, promotes weight gain, and may shorten the length of hospital stay. During postburn rehabilitation, oxandrolone in combination with proper nutrition and exercise increased lean body mass accretion, promoted body weight gain, increased muscle strength, restored patient functional capacity, and shortened the length of rehabilitation. Although oxandrolone effects on serum visceral protein concentrations and bone mineralization have not been evaluated in adult patients with severe thermal injury, studies in pediatric patients with severe thermal injury showed oxandrolone to improve serum albumin, prealbumin, and retinol-binding protein concentrations and to increase bone mineral content.⁴⁹⁻⁵²

Safety

In the above-discussed clinical studies of patients with severe thermal injury, oxandrolone was well tolerated. Mild asymptomatic and reversible increases in serum AST, ALT, and alkaline phosphatase concentrations were reported. No hirsutism, behavioral changes, or virilization were reported. Studies in pediatric patients with severe thermal injury reported clitoromegaly and clitoral hood redundancy that were reversible after oxandrolone discontinuation.⁶⁸⁻⁷⁰ Because the longest duration of continuous oxandrolone therapy in the clinical studies of adult patients with thermal injury was about 4 weeks, the safety of extended oxandrolone therapy in this patient population is unknown. Studies in pediatric patients with severe thermal injury show that oxandrolone is well tolerated for up to 1 year of therapy.⁵⁰

In a retrospective review of 14 adult patients in a burn intensive care unit who were treated with oxandrolone 5 or 10 mg twice/day, no significant difference was noted in hepatic dysfunction (assessed by any increase above baseline of serum AST, ALT, total and direct bilirubin, and alkaline phosphatase concentrations) in patients treated with oxandrolone compared with a historical control group of patients who did not receive oxandrolone.⁷¹ However, study limitations included the inconsistency in measuring and documenting liver function tests, retrospective design, and small sample size. Serum liver transaminase concentrations should be closely

monitored during oxandrolone therapy. Increases in serum transaminase concentrations could indicate oxandrolone-induced liver toxicity. Serum alkaline phosphatase concentrations may not be specific markers of liver toxicity because bone resorption with elevated serum alkaline phosphatase concentrations occur in patients with severe thermal injury.⁶⁸ If serum alkaline phosphatase concentrations become elevated, specific serum alkaline phosphatase liver and bone activities should be measured. Oxandrolone should be discontinued whenever significant or persistent elevation of serum liver function tests occurs, or when potentially serious adverse effects are suspected. Although oxandrolone does not undergo extensive liver metabolism, oxandrolone should be avoided in patients with hepatic insufficiency because of its risk of liver toxicity. Because the elimination half-life of oxandrolone is longer in the elderly who also have greater susceptibility to oxandrolone-induced liver toxicity and fluid retention, a lower oxandrolone dose of 5 mg twice/day is recommended in the elderly population.⁴⁶

Concerns have been raised about the possible adverse effects of oxandrolone on prolonging the duration of mechanical ventilation in critically ill surgical patients. In a study of critically ill ventilator-dependent trauma and surgical patients, oxandrolone 10 mg twice/day significantly prolonged the duration of mechanical ventilation and was associated with a higher rate of reintubation.⁷² The investigators hypothesized that longer ventilator dependence could possibly be related to oxandrolone increasing collagen deposition in the lungs during the later stage of the acute respiratory distress syndrome, causing lung fibrosis and leading to delayed pulmonary recovery. Although this study did not include patients with thermal injury, close monitoring of patients' respiratory function and ventilator dependence is required in critically ill patients with thermal injury who receive oxandrolone and who require prolonged ventilator support.

Because anabolic steroids stimulate androgen-sensitive tissues and increase the risk of prostate hypertrophy and prostate carcinoma, patients with severe thermal injury who have a history of malignancies or elevated serum prostate-specific antigen concentrations should not receive oxandrolone.

Cost

The 2008 average wholesale price of oxandrolone

2.5-mg tablets ranged from \$5.25–7.14/tablet, and for the 10-mg tablets from \$17.80–24.20/tablet.⁷³ Thus, use of oxandrolone 10-mg tablets at doses of 10 mg twice/day results in a daily drug cost of \$36–48.

Conclusion

Oxandrolone 10 mg twice/day improves wound healing, restores lean body mass, and promotes body weight gain in adult patients with severe thermal injury. During the postburn rehabilitation period, oxandrolone therapy in conjunction with adequate nutrition and an exercise program improves lean body mass, increases muscle strength, and restores body weight. Close patient monitoring during oxandrolone therapy, especially for liver function, is recommended. Although data on the efficacy and safety of oxandrolone in adult patients with severe thermal injury are derived from prospective, randomized, controlled studies, limitations are that they mostly originated from a single study center, had relatively small numbers of subjects enrolled, were usually nonblinded, and did not describe institutional review board approval or patient consent. Well-designed, large, multicenter, prospective, randomized studies are needed to better define the optimal oxandrolone dosage, and confirm the safety and efficacy in adult patients with severe thermal injury.

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