The Efficacy of Octreotide in the Therapy of Severe Nonproliferative and Early Proliferative Diabetic Retinopathy

A randomized controlled study

Maria B. Grant, MD
Robert N. Mames, MD
Constance Fitzgerald, MD
Kaushik M. Hazariwala, MD

Rhonda Cooper-DeHoff, pharmd
Sergio Caballero, bs
Kerry S. Estes, phd

OBJECTIVE — The pilot study examined the ability of octreotide to retard progression of diabetic retinopathy (DR) and delay the need for panretinal photocoagulation (PRP) in patients with advanced stages of retinal disease.

RESEARCH DESIGN AND METHODS — Patients with severe nonproliferative DR (NPDR) or early non–high-risk proliferative DR (PDR) were randomly assigned to conventional diabetes management (control group, 12 patients) or to treatment with maximally tolerated doses of octreotide (200–5,000 µg/day subcutaneously; 11 patients). Ocular changes in each eye were assessed at a minimum of every 3 months for 15 months or until disease progressed to high-risk PDR requiring laser surgery. Endocrine assessments occurred at 3-month intervals during the study.

RESULTS — Only 1 of 22 eyes from patients treated with octreotide reached high-risk PDR requiring PRP, compared with control patients, in whom 9 of 24 eyes required PRP. The decreased incidence of progression requiring laser surgery was statistically significant if events were considered independently ($P < 0.006$). The incidence of ocular disease progression was only 27% in patients treated with octreotide compared with 42% in patients with conventional diabetes management. This treatment effect on whether the retina worsened approached statistical significance using repeated measures analysis ($P = 0.0605$). Endocrine management was similar between treatment groups. Thyroxine replacement therapy was administered to maintain a euthyroid state for all octreotide-treated patients and 7 of 12 control patients.

CONCLUSIONS — Our results suggest that octreotide treatment in euthyroid patients may retard progression of advanced DR and may delay the time to laser surgery.

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An important role for growth hormone (GH) in diabetic retinopathy (DR) was indicated 40 years ago when Poulsen (1) described DR regression in a postpartum woman with spontaneous pituitary infarction and proposed hypophysectomy to treat the disease. Subsequent controlled clinical trials showed that pituitary ablation could improve DR. Data from these trials indicated that therapeutic success was correlated with the magnitude of GH decrease (2). Several reviews discuss evidence linking increased GH with DR (3–5). Support for the GH hypothesis includes: 1) the observation that retinopathy accelerates during puberty when tissue sensitivity to GH is increased; 2) diabetic patients with hemochromatosis and infiltrative destruction of the pituitary have little eye disease; and 3) GH-deficient dwarfs with diabetes have no evidence of either macro- or microvascular disease. Even diabetic patients with adequate glucose control show excess GH profiles (6), and DR correlates with the magnitude of GH hypersecretion (7).

The underlying mechanisms of disease progression remain incompletely understood. An increasing body of evidence, however, points to peptide growth factors as key players in microvascular disease. Several peptide growth factors have been identified in the cascade of events resulting in neovascularization that is a hallmark in DR. Current studies are identifying mechanisms through which IGF-I, vascular endothelial growth factor, and other factors mediate effects on angiogenesis (8–11). Several clinical studies support a role for IGF-I in development of retinal neovascularization. Merimee et al. (12) found increased serum IGF-I levels from patients with rapidly accelerating DR. A subsequent prospective study showed that patients had elevated serum IGF-I levels at the time new retinal vessels first appeared compared with their serum IGF-I levels 3 months before the onset of retinal neovascularization (13). In a large population-based study of 928 diabetic patients, higher levels of systemic IGF-I were correlated with an increased frequency of proliferative retinopathy (14).
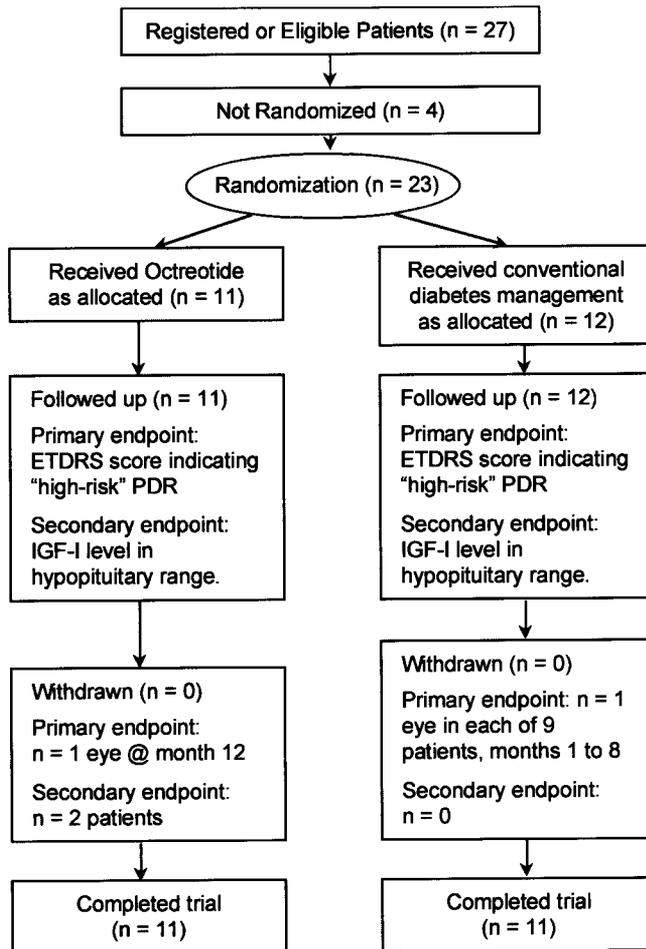
Figure 1—Profile of the randomized controlled study of the efficacy of octreotide in the therapy of proliferative diabetic retinopathy (PDR). The diagram shows the flow of the participants through stages of the trial and timing of primary and secondary outcome measures. All patients who were randomized into the two arms completed the study protocol, although six of those patients required intervention in the form of PRP to one or both eyes as a result of that eye exhibiting high-risk PDR characteristics (see RESEARCH DESIGN AND METHODS for evaluation criteria).

clinical study was designed to extend the 8-week study duration previously examined by McCombe et al. (17) to 15 months using maximally tolerated doses of octreotide administered by constant infusion or with subcutaneous injection 4 times a day with doses up to 5,000 µg/day.

RESEARCH DESIGN AND METHODS— Figure 1 schematizes the trial design. For this trial, 23 patients with type 1 or type 2 diabetes and diagnosed with either severe NPDR or non–high-risk PDR in at least one eye were enrolled between 1993 and 1995 into the study. Subjects were recruited from patients treated for diabetes at the University of Florida Adult Endocrinology clinics and referrals from community retinal specialists. All patients provided written informed consent to participate in required study procedures.

Volunteers were randomized to receive conventional diabetes management alone (control group) or octreotide treatment with conventional diabetes care. Octreotide was administered via subcutaneous injection 4 times a day or via continuous subcutaneous infusion with doses individually adjusted to the highest tolerated somatostatin analog levels. The intent was to increase the dose of octreotide until serum IGF-I was decreased to the hypopituitary range of 75 ng/ml or drug-related adverse effects limited octreotide dosing. The open-label study was designed to continue for 15 months with early termination required if both of the patient's eyes showed disease progression to high-risk PDR. Two eyes from each of the 23 subjects were included in the analysis. It was expected that ~35–50% of eyes in the control group would progress to photocoagulation within the 15-month period (20).

Subjects were evaluated at a minimum of every 3 months for ocular changes using procedures established in the Early Treatment Diabetic Retinopathy Study (ETDRS), with the retinal specialist masked to study treatment (21). Patients were instructed not to discuss medications with the retinal specialists. Ocular examination included stereoscopic fundus photographs using standard photographic fields and angiography. Photographs were assessed by retinal specialists for severity of retinopathy using an extension of the modified Airlie House classification scheme. Severe NPDR required the presence of at least two ETDRS level 47 characteristics. Level 47 characteristics include venous beading in one quadrant,

The GH inhibitory and antiproliferative effects of somatostatin analogs stimulated several clinical trials in severe proliferative DR (PDR) (15,16). Initial clinical results did not consistently show significant efficacy, but the studies were limited to a short dosing duration and doses were often inadequate to suppress GH or IGF-I levels. More promising results were reported when a stabilized somatostatin analog was administered via continuous infusion pump for 4 weeks. The study enrolled a total of 17 patients with early, non–high-risk PDR, and 8 of 11 subjects completed the dosing schedule with somatostatin analog. Disease progression halted in all patients during somatostatin analog treatment (and disease regressed in two patients) whereas disease progressed in half of the six control subjects

(17). Visual acuity improved during several months of continuous infusion with the commercially available somatostatin analog octreotide in an uncontrolled clinical trial with four patients (18).

These results prompted us to initiate a prospective trial comparing maximally tolerated doses of octreotide administered for a prolonged period with conventional diabetes management. The study was designed to address the question, "Can chronic octreotide therapy delay or prevent the progression from either severe nonproliferative diabetic retinopathy (NPDR) or early, non–high-risk proliferative DR to high-risk PDR?" Previous studies demonstrated that continuous infusion of somatostatin analogs resulted in greater suppression of GH than did intermittent injections (19). The current

Table 1—Patient demographic characteristics and clinical parameters

Patient/sex	Diabetes type	Diabetes duration (years)	IGF-I (enrollment/ termination) (ng/ml)	HbA$_{1c}$ (enrollment/ termination) (%)
Octreotide treatment group				
JR/M	1	18	482/137	9.2/7.8
SS/F	1	10	382/107	9.6/8.1
AJ/M	1	15	294/110	8.4/7.0
MJ/M	1	20	210/75	8.0/6.4
MD/F	1	22	285/137	8.4/6.2
HK/F	1	24	202/208	8.0/7.6
DS/F	1	19	169/102	8.4/7.2
HD/F	2	21	234/75	8.9/7.1
BW/F	2	24	291/210	6.8/6.2
WD/M	2	12	214/117	8.3/6.8
JA/M	2	15	201/172	7.4/7.2
Mean	—	18.3	270/132	8.3/7.1
SD	—	4.7	89/46	0.8/0.6
Control treatment group				
CW/M	1	20	453/469	9.0/8.9
DA/F	1	21	326/401	8.2/8.4
GP/M	1	15	402/381	9.3/8.6
KW/M	1	24	482/301	8.1/8.0
IG/M	1	26	261/294	7.9/8.2
BM/M	1	20	201/346	8.0/8.2
JH/F	2	24	129/148	7.2/8.1
MS/M	2	27	201/224	7.9/8.2
HW/M	1	18	324/301	9.2/8.8
JS/F	1	21	428/382	7.2/8.1
KS/F	2	25	283/203	9.0/8.4
LG/F	2	15	168/209	9.2/7.1
Mean	—	22.1	305/303	8.4/8.3
SD	—	4.0	117.7/94.3	0.7/0.4

intraretinal microvascular abnormalities in two to three quadrants, or extensive retinal hemorrhages/microaneurysms. Numeric scores were assigned for severity of DR using the ETDRS criteria at the beginning and end of the study (21). Inclusion criteria required an ETDRS score of 53A or greater in at least one eye. Inclusion criteria also required understanding the study protocol and willingness and ability to participate in required study procedures including frequent ocular examinations. Exclusion criteria included current use of tobacco products, regular medication other than prescribed antidiabetic agents and thyroxine, history of psychiatric illness, illicit drug use, sitting diastolic blood pressure values >80 mmHg, creatinine clearance <30 ml/min, and a BMI that differed by >20% from normal published ranges for the subject's height and sex.

A total of 12 patients were randomized to the control group with conventional diabetes management. The treatment group included 11 patients given continuous infusion or 4-times-a-day subcutaneous injection of octreotide at maximally tolerated doses. Maximally tolerated octreotide doses ranged from 200 to 5,000 μg/day. Mean duration of diabetes did not differ between patients assigned to control (18.4 ± 4.7 years) or treated (21.3 ± 4.0 years) groups. Patients were assessed for ophthalmic and biochemical parameters at the beginning of, at a minimum of 3-month intervals during, and at the end of the 15-month trial. HbA$_{1c}$ was monitored as an index of glycemic control. All patients were clinically euthyroid throughout the study with 7 of 12 conventionally managed patients requiring thyroxine (Synthroid) treatment. Thyroxine was added to ensure clinical euthyroid status in all octreotide-treated patients, because of the inhibitory effects of the drug on thyrotropin-stimulating hormone (TSH) secretion. Demographic characteristics of the patients are listed in Table 1.

Statistics

Results were evaluated with the aid of Statistical Analysis System (SAS) software. The two-tailed t test was used to evaluate differences between the control and treatment groups for quantitative parameters. These parameters included duration of diabetes at enrollment, change in IGF-I, and change in HbA$_{1c}$. The Kaplan-Meier product limit method was used to generate survival curves for time surviving without need for panretinal photocoagulation (PRP) for each eye. The difference between treatment groups was compared using a log rank nonparametric test of significance between the curves. Fisher's exact test was used to test for significant differences in the incidence of PRP between the treated and control groups. In addition to evaluating the time surviving without need for PRP, a repeated measures analysis was used to test for fixed effects from treatment for each eye on the change from baseline in the ETDRS score during the course of the study. The repeated statement in the program of the SAS software used in analysis included fitting a generalized estimating equation model. Since the ETDRS score was not truly continuous, the changes in baseline scores were predominantly zeros for the treatment group and showed more variation in the control group. Logistic regression was conducted to test whether the treatment affected the ETDRS score. The measurements on the two eyes of each patient were considered correlated in the repeated measures model.

RESULTS — All 23 patients enrolled completed the study protocol. As shown graphically in Fig. 2, only 1 of 22 eyes from octreotide-treated patients required PRP during the study period, in month 12 of the study. In conventionally managed patients, 9 of 24 eyes required PRP between month 1 and 8 of the study. When the Kaplan-Meier product limit method was used to generate survival curves for the incidence of disease progression in the octreotide-treated and control groups, there was a significant difference detected for the PRP-free versus time profiles between groups (P < 0.006). Although the percent of patients requiring PRP surgery in the control group was 42% compared with 9% in the octreotide-treated group, this difference was not statistically significant at the 0.05 level. The primary end point in this study was disease progression to require PRP in each eye (22). PRP was performed at an ETDRS score of

Figure 2—Survival curves showing the percentage of eyes that did not reach high-risk PDR status as defined by ETDRS scores of 71 or 75 throughout the duration of the study. When such a score was attained, that eye underwent PRP and was no longer evaluated for the rest of the study period. Eyes (control, $n = 24$) from conventionally managed patients demonstrated significantly lower survival ($P = 0.006$) than eyes (OCT, $n = 22$) from patients treated with maximally tolerated long-term octreotide.

tistically significant at the 95% confidence level, the data support further investigation.

At least three mechanisms have been proposed for the antiproliferative effects of somatostatin (23). Somatostatin receptor activation stimulates tyrosine phosphatase and may reverse the growth promotion of the tyrosine kinase group of oncogenes to alter antiproliferative cell signaling. In vitro studies showed that the somatostatin analogs activate protein tyrosine phosphatases and therefore function at the biochemical level by promoting inactivation of the autophosphorylated growth factor receptor (24,25). Somatostatin may directly inhibit steps in the cascade of events resulting in angiogenesis. Our studies conducted in rapidly proliferating human retinal endothelial cells that were stimulated with IGF-I and basic fibroblast growth factor (bFGF) in vitro demonstrated direct inhibitory effects of octreotide in these cells (26). Alternatively, the antiproliferative effects of somatostatin could be attributed exclusively to inhibiting secreted GH, IGF-I, and other secreted hormones involved in growth.

Vitreous levels of IGF-I better reflect the local levels of growth factors seen by retinal tissue. Our earlier study measured IGF-I from vitreous samples collected in 23 diabetic patients with PDR compared with age-matched control values (27). A threefold increase was observed in the DR samples compared with control subjects. IGF-I secretion was augmented by bFGF in cultured human retinal endothelial cells, which supports a paracrine role (26). The finding that vitreous concentrations of IGF-I are significantly increased in diabetic

71 or 75 that corresponded to high-risk PDR with extensive neovascularization. The control group had a more pronounced difference in the ETDRS score change from baseline of 7.1 ± 11.2 compared with the mean score change in octreotide-treated subjects of 0.9 ± 4.5 units, which is illustrated in Fig. 3. However, the repeated measures analysis difference between groups for the change in ETDRS score from baseline did not achieve statistically significant difference at the 95% confidence level, with a P value of 0.0605.

Octreotide significantly suppressed serum IGF-I values from a mean value of 270 ± 93 ng/ml at the beginning of octreotide treatment to 132 ± 47 ng/ml at study termination ($P < 0.05$), with 2 of 11 patients suppressed to hypophysectomized levels of <75 ng/ml. IGF-I values were unchanged over the treatment period in conventionally managed patients, with means of 305 ± 118 ng/ml at enrollment and 303 ± 94 ng/ml at study termination. There was no difference in IGF-I levels before drug treatment between treated and untreated patients. HbA_{1c} improved in octreotide-treated patients from $8.6 \pm 0.8\%$ at enrollment to $7.2 \pm 0.6\%$ at study termination. Control patients did not change HbA_{1c} values, with a mean initial value of $8.4 \pm 0.8\%$ and a final mean value of $8.3 \pm 0.5\%$.

CONCLUSIONS — The results from this pilot study suggest that chronic

octreotide treatment can retard development of high-risk PDR in patients with advanced DR when administered in combination with conventional diabetes management. Disease progressed to require PRP in only 1 of 22 eyes from patients treated with maximally tolerated doses of octreotide compared with 9 of 24 eyes from patients treated with conventional diabetes management over the 15-month study period. The incidence of patients with disease progression to severe PDR was only 9% with octreotide treatment compared with 42% in conventionally managed patients during the 15-month trial period. Although this difference was not sta-

Figure 3—Change in ETDRS score for each eye from data collected at patient enrollment compared with study completion.

patients with neovascularization was independently confirmed (28). Studies in animal models of ocular neovascularization indicate the significance of GH and IGF-I in retinal disease. Intravitreal IGF-I administration, but not heat-inactivated protein, can reproduce several microvascular abnormalities that are found in DR, including increased basement membrane thickening, severe hyperemia with vascular engorgement, tortuosity, intraretinal hemorrhage, and endothelial cell proliferation (29,30).

In apparent contrast to the simple hypothesis that increased IGF-I mediates aberrant neovascularization, several studies showed that circulating IGF-I levels are inappropriately low in most patients with type 1 diabetes given their higher-than-normal GH levels (31,32). This observation in type 1 diabetic patients is due in part to lack of portal insulin, which stimulates hepatic IGF-I secretion. The ability of IGF-I to lower glucose and abnormal GH/IGF-I/IGF binding protein system identified in diabetic patients led to use of recombinant human IGF-I (rhIGF-I) to treat hyperglycemia in diabetic patients (33). However, the doses of rhIGF-I required to improve hyperglycemia may be limited by adverse effects. Among the most serious of these adverse effects from rhIGF-I treatment is progression of DR (34). A recent report identified two cases of retinal changes mimicking DR in nondiabetic patients treated with GH-dosing regimens that would be expected to increase IGF-I (35).

Results from previous clinical studies that examined the efficacy of somatostatin analogs in treating DR were inconclusive or showed no therapeutic effect (15,16,36). Interestingly, a trial examining the ability of long-term octreotide treatment to improve early DR identified mild hypothyroidism in patients infused for 1 year with 400 μg/day of the somatostatin analog but found no evidence for clinical significance of the hypothyroidism (36). Results of their trial with early DR found no difference between retinal disease in conventionally managed patients and octreotide-treated patients. Similarly, our previous study with 16 patients with type 1 diabetes found no difference in progression of DR between groups of 8 patients randomly assigned to conventional diabetes management and 8 patients assigned treatment with maximally tolerated doses of octreotide in conjunction with routine diabetes management (37). In our initial 15-month study, octreotide doses of 500 μg/day were escalated based on IGF-I lev-

els and drug tolerance to a maximum dose that ranged from 600 to 3,000 μg/day during the 15-month treatment period. A 5-day evaluation period was included with patients confined to the clinical research unit at study initiation, at which time octreotide was administered as a constant subcutaneous infusion and GH secretion was quantified from area under the serum concentration versus time curve for blood samples collected every 2–4 h throughout a 24-h period. Mean IGF-I levels decreased 40% in the group of 8 octreotide-treated patients and was unchanged in the group of 8 conventionally managed patients (37). Thus, IGF-I inhibition alone cannot readily explain the effects of octreotide on progression of DR. Improved glycemic control was also achieved in our earlier study after octreotide with mean HbA_{1c} levels of 6.4 ± 0.9% in octreotide-treated patients compared with mean values of 8.1 ± 1.8% in conventionally managed patients. Because both groups had an identical incidence of PRP, improved glycemic control does not appear to explain octreotide efficacy. However, studies with larger subject populations could better define the potential contribution of improved glycemic control on disease progression.

One difference between the current study design and our previous trial with octreotide was endocrine management to maintain euthyroid status in all patients. It is well recognized that somatostatin analogs decrease TSH secretion. Although chronic octreotide does not appear to alter thyroid function in acromegalic patients (38), the drug resulted in decreased TSH secretion in patients without excess GH secretion (39). Several studies have shown TSH inhibition with various regimens of somatostatin analogs (36,40). However, long-term octreotide administration often had no reported effect on circulating thyroid hormones (39,41). Endocrine management in the current study included thyroid hormone replacement in 18 of the 23 patients compared with 4 of the 16 patients enrolled in the previous study. ETDRS scores at patient enrollment were similar for each study.

Hypothyroidism could impair the antiproliferative effect of somatostatin through several mechanisms that may be clinically relevant for treatment with octreotide or other long-acting analogs. Our clinical results showing similar degree of IGF-I inhibition in patients receiving octreotide with thyroid hormone (phase II) or octreotide alone (phase I) suggest that the degree of secreted hormone suppression

measured in the circulation does not account for improved efficacy of octreotide in DR.

Retinal neovascularization and chronic retinal edema associated with severe DR threaten vision. PRP is currently the only accepted treatment option for severe high-risk DR. The effectiveness of PRP may be due to the inhibitor of aberrant capillary vessel formation via the destruction of ischemic retinal tissue, which is the source of growth factors implicated in angiogenesis. Although recent elegant studies in various animal models suggest that selectively altering just one of the growth factors involved in angiogenesis could effectively retard neovascularization, no effective therapeutic alternatives to retinal tissue destruction have been identified (8,11). Interestingly, a recent report documented the efficacy of octreotide in treating macular edema that was refractory to anti-inflammatory drugs and acetazolamide (42).

Our results in 23 patients with advanced stages of DR indicate that octreotide may retard the progression of the vision-threatening disease. Maintenance of the euthyroid state in conjunction with chronic octreotide treatment appears to be a newly observed contributing factor to efficacy of the somatostatin analog. Investigations that elucidate potential roles of thyroid hormone function on intracellular signaling may improve understanding of this apparent potentiation of octreotide activity.

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