

Treatment of DR With Somatostatin Analogues: *Where Do We Go From Here?*

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Prevention is the best approach to diabetic retinopathy. Intensive glucose management can delay onset and progression of retinopathy in diabetic patients,¹⁻³ particularly in combination with hypertension and lipid control.^{3,4} In patients failing this approach, panretinal photocoagulation (PRP) is both clinically effective and cost-effective in managing proliferative diabetic retinopathy (PDR). Pharmacological approaches may represent an alternative to PRP in selected patients and may be used in combination with PRP in patients who have failed PRP alone.

PDR pathogenesis is multifaceted.⁵ Pharmacological therapies targeting multiple PDR mechanisms may provide more efficacious treatment strategies. The best studied approaches include protein kinase C (PKC) inhibition,⁶ improvement of endothelial precursor function^{7,8} and growth hormone (GH) and growth factor antagonist.⁹

SOMATOSTATIN THERAPY

A promising area of pharmacological research is GH/insulin-like growth factor-1 (IGF-1) blockade with synthetic analogues of somatostatin (SST). SST is a neuropeptide with reported potent inhibitory effects on pituitary GH secretion.¹⁰ SST has multiple functions, acting via five G-pro-

tein coupled receptor subtypes SSTR1-5¹¹ and affecting hormone secretion, neurotransmission, cell proliferation, smooth muscle contraction, nutrient absorption, inflammation and angiogenesis. SST was found in markedly reduced levels in the vitreous of PDR patients with active neovascularization,¹² suggesting that it is an endogenous antiangiogenic factor. Short circulation half-life and multifaceted systemic effects have limited the therapeutic use of the natural peptide.

Sandoz (Basel, Switzerland) initiated a program for development of long-acting SST analogues. This led to synthesis of octreotide (SMS 201-995),¹³ a compound-inhibiting GH, glucagon and insulin secretion more actively than native SST with a half-life of 2 hours after subcutaneous administration (Figure 1). Octreotide (Sandostatil;

Sandoz, Basel, Switzerland) was approved by the US Food and Drug Administration for the treatment of acromegaly and the symptomatic treatment of diverse hypersecretory neuroendocrine tumors.^{14,15}

GH-hypersecretion was linked to retinopathy when it was observed that a diabetic patient with PDR had spontaneous resolution of her neovascularization following post-partum pituitary infarction.¹⁶ DR progression was delayed by controlling excess GH¹⁷⁻¹⁹ through pro-

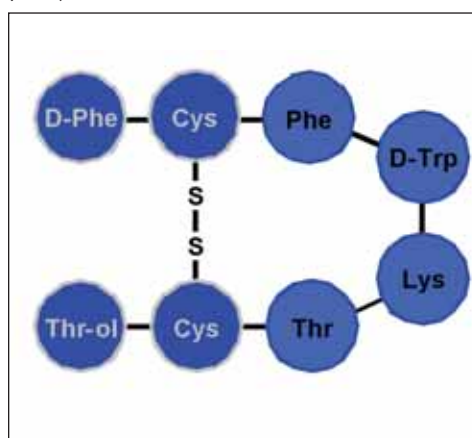


Figure 1. Structure of octreotide (SMS 201-995).

cedures such as hypophysectomy, pituitary yttrium implantation and alpha-particle pituitary radiation. The degree of retinopathy regression was proportional to the degree of GH deficiency achieved. GH-deficient dwarfs with diabetes were free of microvascular complications over the course of 3 decades.²⁰ There was a reduced retinopathy incidence in diabetic patients with hemochromatosis and pituitary dysfunction.²¹

The mediator of GH's mitogenic actions is IGF-1. Increases in serum IGF-1 preceded the acute progression of retinopathy in a prepubertal patient with chronic insulin deficiency.²² Intense insulin therapy increased serum IGF-1 between 70% and 220% and worsened retinopathy.²³ This observation was independently confirmed in patients in the Diabetes Control and Complications Trial (DCCT) on intensive insulin management.^{24,25} It was hypothesized that increasing insulin therapy and improving blood glucose control in a poorly controlled individual leads to liver insulinization (ie, increased hepatic IGF-1 production and retinal neovascularization).^{23,26}

Octreotide inhibited growth factor-stimulated proliferation and migration in endothelial cells.²⁷ The direct antiproliferative effect of octreotide includes cell cycle arrest via SSTR2, apoptosis via SSTR3 stimulation¹¹ and SSTR1-mediated effects on angiogenesis.²⁸

Octreotide was efficacious in the oxygen-induced retinopathy (OIR) model.²⁹ Systemic octreotide injection in rats with variable hyperoxia exposure, however, did not significantly reduce retinal neovascularization.³⁰ These data suggest that systemic administration of SST analogues does not always result in sustained therapeutic reduction of circulating IGF-1 levels, and subsequent local treatment may be necessary. Additionally, long-term therapy leads to desensitization.³¹

Several nonpeptide SSTR2 agonists with potencies comparable with octreotide have been developed. They inhibited retinal neovascularization in a dose-dependent manner when given systemically in the OIR model and intravitreally in the choroidal neovascularization model.³²

CLINICAL TRIALS USING OCTREOTIDE

In 1999, Novartis initiated two phase 3 multicenter, randomized, double-masked, placebo-controlled studies in moderate-to-severe nonproliferative DR (NPDR) and low-risk PDR patients. They included the largest-ever cohort of patients who were at moderate-to-high risk of progressing to vision-threatening PDR within the study time frame. The patients received therapy for an average 4 years, with a maximum treatment duration of 6 years. Ophthalmologic assessments included visual acuity measurements and semiquantitative, stereoscopic, seven-field, color, 30° Early

Treatment of Diabetic Retinopathy Study (ETDRS) fundus photography. The Wisconsin Central Reading Center graded the fundus photographs according to ETDRS criteria. The primary outcome was DR progression as defined by the ETDRS retinopathy severity scale for one or two eyes. Key secondary outcomes included change in overall visual acuity that was defined as time to loss of ≥ 15 letters on the ETDRS visual acuity scale and changes in macular edema between baseline and follow-up visits. Drug safety and tolerability were also carefully monitored.

Importantly, both studies had similar distribution of retinopathy severity on the ETDRS scale with 20% to 25% of patients already at low-risk PDR at study entry — and similar distribution of ETDRS-rated visual acuity. Most patients scored within or above 70 to 84 letters, whereas approximately 20% scored within or below 55 to 69 letters.

The demographics and baseline characteristics were comparable between the two studies. In Study 804, however, patients had higher body mass index (two units), and more patients had neuropathy, cataracts, macular edema and photocoagulation at study entry. The Study 804 octreotide group included fewer smokers, and the placebo group dis-

TABLE 1. SUMMARY OF OCTREOTIDE CLINICAL TRIALS CONDUCTED BY NOVARTIS

Parameters	Study 802	Study 804
Number of participants	585	313
Number of testing sites	61	36
Location	Europe	North America, Brazil
Treatment groups	Placebo, 20 mg and 30 mg octreotide LAR	Placebo and 30 mg octreotide LAR
Progression to retinopathy	No change vs control 30 mg (<i>P</i> =.9067) 20 mg (<i>P</i> =.9436) 30 mg vs.20 mg (<i>P</i> =.9073)	Delayed (<i>P</i> =.00430) 30 mg vs control
Progression to macular edema	No change vs control 30 mg (<i>P</i> =.7245) 20 mg (<i>P</i> =.9751) 30 mg vs 20 mg (<i>P</i> =.7242)	No difference vs control (<i>P</i> =.8751)
Loss of visual acuity on ETDRS scale	Delayed 30 mg vs control (<i>P</i> =.0032) No change 20 mg vs control (<i>P</i> =.6360); 30 mg vs 20 mg (<i>P</i> =.1137)	No difference vs control (<i>P</i> =.1054)

continued at a lower rate. In Study 804, the time to progression of retinopathy, but not the time to development/progression of macular edema, was significantly delayed in the octreotide group (Table 1).

In Study 802, octreotide had no significant effect upon the time to progression of retinopathy or macular edema; but visual acuity loss was delayed in the 30-mg group (Table 1). In both studies, octreotide groups had reduced serum IGF-1 levels with fewer patients needing vitrectomy compared with control. In conclusion, the primary objective was achieved in Study 804 – octreotide LAR (30 mg) delaying the time to progression of retinopathy. Visual acuity improvement showed a strong trend in both trials. The adverse event profile was similar to that reported with subcutaneous octreotide.

DISCUSSION

SST analogues are safe and effective for the treatment of severe diabetic retinopathy, however, clinical results with octreotide for DR have been variable but furnished some critical information. Good results were observed in patients with severe NPDR and low-risk PDR receiving high dosage regimens. Also, patients with ischemic eyes and iris neovascularization responded particularly well to octreotide, possibly due to the IGF-1–driven character of the condition. The need for high doses in some patients suggests a direct effect on SST receptors (SSTRs) in ocular tissues. Systemic octreotide may inadequately penetrate the blood retinal barrier (BRB). Local administration of SST analogues could be a better approach. Additionally, it is crucial to identify the most responsive patient populations.

For optimal systemic effect, the drug must cross the BRB, and drug levels in the retina must be high enough to diffuse to the ischemic areas, preventing the release of proangiogenic factors and subsequent neovascularization. While octreotide blocks local and systemic production of proangiogenic GH and IGF-1, studies also support that retinopathy cessation and/or regression with improvements in visual acuity may occur without significant changes in serum GH or IGF-1 levels. Thus, the autocrine and paracrine effects of SST may be particularly important, as SST analogues can act directly on retinal endothelial cells and RPE cells, which are known to express SSTRs.

Clinical trial results support the use of octreotide long-acting release (LAR) for patients with advanced disease to decrease vision impairment. Octreotide LAR remains the only therapeutic alternative for patients who fail PRP. A better understanding of retinal SSTR pharmacology and of retinopathy will allow optimization of future PDR treatment. ■

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