

Vitrase Effective for Vitreous Hemorrhage Management

Statistically significant outcomes were seen as early as the month of treatment.

BY BARUCH D. KUPPERMANN, MD, PhD

Highly purified ovine hyaluronidase (Vitrase; Ista Pharmaceuticals, Irvine, Calif) is a therapeutically efficacious treatment option for the management of vitreous hemorrhage.¹

Vitreous hemorrhage, a major vision-threatening problem, occurs in seven per 100,000 people each year in Europe. If the statistics are similar in the United States, then about 20,000 new cases of dense spontaneous hemorrhage occur annually.

The most common cause of vitreous hemorrhage is complication from proliferative diabetic retinopathy (PDR). There are other causes such as branch or central retinal vein occlusion, posterior vitreous detachment with or without retinal tear or detachment and ocular trauma.

PATHOLOGIC FOUNDATION

It is thought that the pathologic foundation of vitreous hemorrhage in retinal vascular disease is the development of retinal ischemia that induces retinal neovascularization. The new abnormal blood vessels that develop grow into the vitreous cavity, using the vitreous as a scaffold. The vitreous traction on these new vessels results in vitreous hemorrhage.

Patients with type 1 diabetes have a higher risk of developing PDR than those with type 2 diabetes. These patients therefore have more frequent and more severe ocular complications. Early visualization of the reti-

TABLE 1. BASELINE DEMOGRAPHICS FROM THE POOLED VITRASE STUDY

	Vit-02 (n=750)	Vit-03 (n=556)	Integrated (n=1,125)
Gender			
Male	52.4%	50.2%	51.6%
Age* (mean years)	61.9	61.9	62.0
Ethnicity			
white	50.8%	84.0%	67.6%
black	5.5%	9.7%	7.7%
Asian	3.5%	3.6%	3.5%
other	40.1%	2.7%	21.2%
Diabetes Status			
nondiabetic	17.3%	28.6%	23.7%
diabetic	82.7%	71.4%	76.3%
type 1	52.9%	69.3%	59.4%
type 2	47.1%	30.7%	40.6%
BCVA			
unable to read any letters on the eye chart	86.9%	95.0%	90.4%
Hemorrhage Duration			
days mean (SD)	116.9 (104.6)	125.3 (113.0)	120.4 (110.0)

*For Vit-02, age and gender data were missing for one patient randomized to 55-IU treatment. One patient randomized to saline had a calculated age that resolved to 0 because of missing information. In Vit-03, three patients had missing birth years, and one patient had a missing gender value. These patients were not included in the age or gender calculations.

Source: Am J Ophthalmol. 2005;140:573-584.

na to identify and treat the underlying causative disorder is critical to maximize the return of visual function.

My colleagues and I recently reported our study in the *American Journal of Ophthalmology*. We pooled results from two multinational, randomized, double-masked, controlled trials of intravitreal injection of ovine hyaluronidase. Patients included in the phase 3 trials had vitreous hemorrhage \geq 1 month that was severe at entry and BCVA worse than 20/200.

SEE UNDERLYING PATHOLOGY

To determine efficacy, clearance of the hemorrhage had to be sufficient enough to see the underlying pathology and completion of the treatment when indicated. This was measured at months 1, 2 and 3. The key secondary endpoints included \geq 3-line improvement in BCVA, hemorrhage density reduction and therapeutic utility assessment.

The patients were randomized to receive 55 IU or 75 IU of ovine hyaluronidase or saline.

The intention-to-treat population was 1,125 patients; at baseline, 76.3% had diabetes, 90.4% were unable to read any letters on the eye chart, and the mean hemorrhage duration was 120 days (Table 1).

We found that statistical significance was reached in the patients assigned the 55-IU dose by months 1 and 2 for the primary efficacy endpoint using an adjusted *P*-value. By treatment months 1, 2 and 3, 13.2%, 25.5% and 32.9% of the patients in the 55-IU dose group reached primary efficacy compared with 55%, 16.2% and 25.6% of patients who were assigned saline (*P*<.001, *P*=.002, *P*=.025, respectively).

The treatment effect was confirmed by the key secondary endpoints at both doses and all time points (*P*≤.01).

POOLED SAFETY DATA

In the pooled safety data, published in the same journal, no serious safety issues were reported after the single injection. Retinal detachment incidence was not statistically different between treatment and placebo groups, with iritis manifesting as an acute self-limited inflammation as the most common adverse event. This occurred in a dose-response fashion, but was not noted to result in a serious adverse event in any treated eye.²

These studies were the first of their kind to evaluate the efficacy of an enzymatic agent for the management of vitreous hemorrhage. The management options currently available are observations and pars plana vitrectomy. Enzymatic vitreolysis offers several potential advantages over the current standard practice, including the ability to diagnose and treat the eye earlier, at a lower cost and with greater patient availability.

TABLE 2. CUMULATIVE PERCENTAGES OF PATIENTS ATTAINING \geq 3-LINE IMPROVEMENT IN BCVA BY MONTH 3

	Saline control (n=383)	55 IU (n=365)	75 IU (n=377)
Month 1	20.1%	30.7%	27.9%
Pairwise <i>P</i> -value		<i>P</i> <.001	<i>P</i> =.013
Month 2	27.4%	41.1%	38.2%
Pairwise <i>P</i> -value		<i>P</i> <.001	<i>P</i> =.002
Month 3	34.5%	44.9%	43.5%
Pairwise <i>P</i> -value		<i>P</i> =.004	<i>P</i> =.011

Source: Am J Ophthalmol. 2005;140:573-584.

Although the primary endpoint was to be achieved by month 3, it was seen as early as month 1, the earliest time point at which efficacy was assessed, and through month 2 in a statistically significant proportion of patients treated with a single injection of 55 IU.

KEY SECONDARY ENDPOINTS

We found that the relative difference in the primary efficacy of 55 IU ovine hyaluronidase compared with saline was greater by month 1. Also, the relative difference by month 2 was greater than by month 3. The three key secondary endpoints are corroborative of this finding: The endpoints were reached with statistical significance by month 1 and persisted through month 3 (Table 2).

Although the initial management of vitreous hemorrhage is often conservative, there is evidence that early clearance of vitreous hemorrhage is associated with improved long-term preservations of useful vision and an improved quality of life. For some patients, a nonsurgical option may restore vision at an earlier time point and positively impact their quality of life. ■

Baruch D. Kuppermann, MD, PhD, is in the department of ophthalmology at the University of California, Irvine. Dr. Kuppermann is a member of the RETINA TODAY editorial board. He disclosed that he is a consultant for Ista Pharmaceuticals. He may be reached at bdkupper@uci.edu.

1. Kuppermann BD, Thomas EL, de Smet MD, Grillone LR. Pooled efficacy results from two multinational randomized controlled clinical trials of a single intravitreal injection of highly purified ovine hyaluronidase (Vitrace) for the management of vitreous hemorrhage. *Am J Ophthalmol*. 2005;140:573-584.

2. Kuppermann BD, Thomas EL, de Smet MD, Grillone LR. Safety results of two phase 3 trials of an intravitreal injection of highly purified ovine hyaluronidase (Vitrace) for the management of vitreous hemorrhage. *Am J Ophthalmol*. 2005;140(4):585-597.