

# The importance of pegaptanib sodium treatment for patients with vascular active vitreoretinopathy

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**Abstract.** The aim of the present study was to report the importance of pegaptanib sodium (PGSD) injection treatment for vascular active vitreoretinopathy (VAVR). A total of 82 patients with VAVR diagnosed by increasing subretinal exudation were enrolled and received a single intravitreal injection of PGSD. The efficacies of PGSD for patients with VAVR were analyzed using photography, fluorescein angiography and optical coherence tomography. The pathological changes in vascular activity, amount of exudation and visual acuity between the PGSD, and placebo group were also compared. The results demonstrated that the PGSD injection significantly decreased subretinal exudation and leakage compared with the placebo when assessed using fluorescein angiography in a 12-month follow-up. It was observed that the PGSD injection inhibited inflammatory cytokines interleukin-1 $\beta$  and tumor necrosis factor  $\alpha$  for patients with VAVR compared with the placebo. Furthermore, results demonstrated that the average inflammation score and intraocular pressure was significantly decreased compared with the placebo. Visual acuity was improved from 1.3 to 0.7 in the majority of patients in the PGSD group. In conclusion, the outcomes of the present study indicate that the PGSD intravitreal injection is an efficient treatment option for patients with VAVR.

## Introduction

Vitreoretinopathy is one of the most common retinopathies and is one of the complications of rhegmatogenous retinal detachment retinal detachment surgery (1). There are many clinical manifestations of vitreoretinopathy, such as glass brown granules and grey cells existing in vitreous body,

hyperplasia of proliferative vitreous retinopathy, retinal stiffness and wrinkles, subretinal membranes and tractional detachment of retina (2,3). Researches have showed that retinal detachment with avascularity of the peripheral retina typically is associated with familial exudative vitreoretinopathy, which can cause by mutations of KIF11 and lead to microcephaly, lymphedema, chorioretinal dysplasia, microcephaly, chorioretinal dysplasia and mental retardation (4). Currently, surgeries and drug treatments are efficient way to cure vitreoretinopathy, while vascular active vitreoretinopathy (VAVR) frequently remains one of the most severe complications of rhegmatogenous retinal detachment (RD) with an incidence of 5-11% (5). VAVR also presents one of the most frequent causes of surgical failure for patients with VAVR (6).

Previous report has showed that pegaptanib sodium (PGSD) treatment is efficient for VAVR by decreasing subretinal exudation and leakage determined by fluorescein angiography (7). PGSD is selective vascular endothelial growth factor (VEGF) inhibitor that can decrease the formation of new blood vessels in the choroid and reduce the leakage of pathological changes of the blood vessels (8,9). An exploratory analysis has indicated the efficacy of PGSD for early treatment of nonvascular age-related macular degeneration (10). Interestingly, the therapeutic effects of PGSD for ocular vascular disease also have been reviewed (11). However, the importance of PGSD treatment for patients with VAVR has not been well investigated.

In this study, we investigated the efficacy of PGSD for clinical nursing of VAVR patients. We evaluated the ameliorative effects of PGSD for VAVR patients after surgical treatment. Our investigations suggest that PGSD injection is a potential agent for the treatment of patients with VAVR.

## Materials and methods

**Study design, subjects and sampling.** A total of 82 patients with VAVR were recruited in this retrospective study. All patients were confirmed VAVR by pathophysiology reported previously (12). The age of patient's was 48.8 $\pm$ 12.6 years. Subjects include 42 female patients and 40 male patients. Inclusion criteria for individuals with VAVR were diagnosed by fluorescence fundus angiography. The Institutional Review Board approval was obtained for this study. The study

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protocol was approved by the Central Ethics Committee (Ethics Committee of Center of Tianjin Medical University; Approval number: TJMU20140311EX). Inclusion criteria include patients with rhegmatogenous retinal detachment retinal detachment surgery. Exclusion criteria include patients with no other metabolic disease (such as diabetes mellitus and scurvy). All patients were required to write informed consent with signature.

**Drugs administration.** In total, 82 patients were enrolled in this study and were randomized into two groups based on age and gender match. All of the patients completed the study in 12 months follow-up period. The indicated dosage of ophthalmic solutions was PGSD (0.3 mg, Macugen; Eyetech Pharmaceuticals, New York, NY) or placebo (same amount of normal sodium, Harbin pharmaceutical group, China) injection was used to treat VAVR patients. Patients with VAVR were given 0.3 mg and patients in the placebo group received 0.3 mg sodium solution via intravitreal injection once every six week.

**ELISA.** Serum levels of IL-1 $\beta$  (MBS700340, Thermo Fisher Scientific) and TNF $\alpha$  (MBS6080, Thermo Fisher Scientific) were analyzed in patients with VAVR after received PGSD intravitreal injection or placebo using ELISA kit according to the manufacturer's instrument. The serum concentration levels of IL-1 $\beta$  and TNF $\alpha$  were measured by an enzyme micro-plate reader at 450 nm.

**Inflammation severity score and chamber flare.** Criteria for evaluation were the reduction in anterior chamber flare and inflammation severity score (primary efficacy criteria) as well as different secondary efficacy and safety evaluation criteria. Mean inflammation severity score were evaluated according to previous report (13).

**Intraocular pressure measurement.** Corneal surface intraocular pressure in each patient with VAVR was measured using a Tono-Pen AVIA<sup>®</sup> Applanation Tonometer (Reichert Technologies, USA). To minimize circadian oscillation, intraocular pressure measurement measurements were measured once every 7 days at 12:30 pm in all patients during 12-months follow-up. The intraocular pressure was sorted out by call visits.

**Clinical Assessments.** All measurements were performed by the same technician in two groups during the 12-month follow-up, on day 0 after surgery, 4th, and 12th months. The efficacy of PGSD on aqueous flare, subretinal exudation and leakage, visual acuity and vitreoretinal traction was using methods reported previously (14-16). Each result of clinical assessments was determined based on the mean of five measurements.

**Statistical analysis.** Continuous variables were shown as mean  $\pm$  SD and analyzed by students t test. All data were analyzed using SPSS Statistics 19.0 (version 19.0; SPSS Inc., Chicago, IL, USA) and Graphpad Prism version 5.0 with the help of Microsoft Excel. Unpaired data was determined by Student's t test and comparisons of data between multiple groups were analyzed by variance (ANOVA). A P-value of  $\leq 0.05$  was considered statistically significant.

Table I. Clinical characteristic of patients with VAVR.

Characteristic	Placebo	PGSD	P-value
Number	38	44	>0.05
Gender (male/female)	18/20	23/21	>0.05
Age (years)	36.2-60.4	36.5-61.4	>0.05
Corneal thickness ( $\mu$ m)	527.3 $\pm$ 53.7	526.8 $\pm$ 58.5	>0.05
Inflammation severity	3.4 $\pm$ 0.7	3.3 $\pm$ 0.8	>0.05
Intraocular pressure (mm Hg)	15.2 $\pm$ 3.5	15.4 $\pm$ 3.2	>0.05
Aqueous flare (p/msec)	9.1 $\pm$ 1.8	9.2 $\pm$ 2.0	>0.05

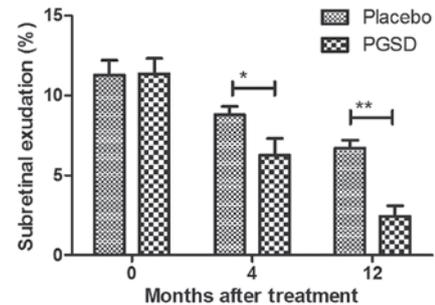


Figure 1. Intravitreal injection of PGSD was decreased in patients with VAVR during 12 months follow-up. PGSD, pegaptanib sodium; VAVR, vascular active vitreoretinopathy.

## Results

**Characteristics of patients with VAVR.** A total of 82 patients with FEVR were enrolled and to analyze the efficacy of PGSD injection treatment. Mean age of patients were 48.8 $\pm$ 12.6 years and 42 patients were female and 40 patients were male. The average inflammation score was 2.5 $\pm$ 1.0 and intra-ocular pressure 12.4 $\pm$ 3.6 mm Hg. Patients were randomly divided into two groups and received a single intravitreal injection of PGSD (10 mg/day) or placebo. The characteristics of patients with VAVR were shown in Table I.

**The efficacy treatment of PGSD intravitreal injection on subretinal exudation and leakage in patients with VAVR.** The efficacies of PGSD injection in on subretinal exudation and leakage were investigated in patients with VAVR after 4 and 12 month treatment. Outcomes presented a significantly reduction of subretinal exudation in patients after receiving treatment of intravitreal injection of PGSD (Fig. 1). We observed intravitreal injection of PGSD markedly decreased leakage by fluorescein angiography in patients with VAVR (Fig. 2). These outcomes suggest that PGSD intravitreal injection were significantly improved subretinal exudation and leakage in patients with VAVR after 12-month treatment, which presented enough benefits compared to placebo and 0- and 4-month PGSD treatment.

**The efficacy of treatment of PGSD intravitreal injection on inflammation and intra-ocular pressure in patients with VAVR.** We evaluated the ameliorative effects of treatment of PGSD intravitreal injection on inflammation and intra-ocular

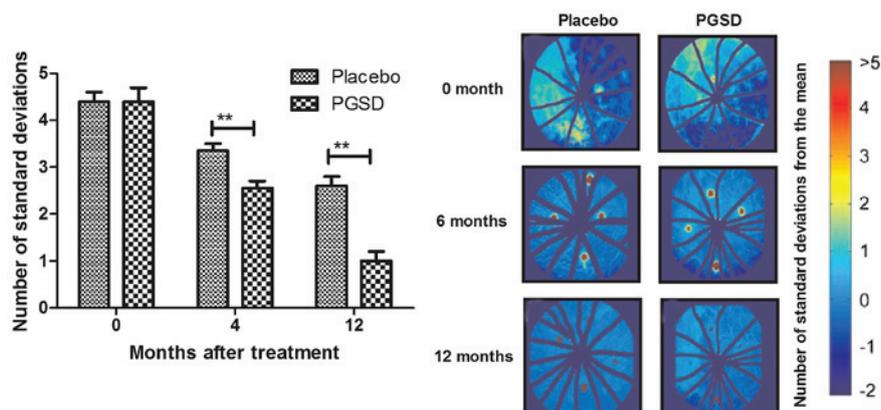


Figure 2. PGSD treatment markedly decreases leakage by fluorescein angiography in patients with VAVR. PGSD, pegaptanib sodium; VAVR, vascular active vitreoretinopathy.

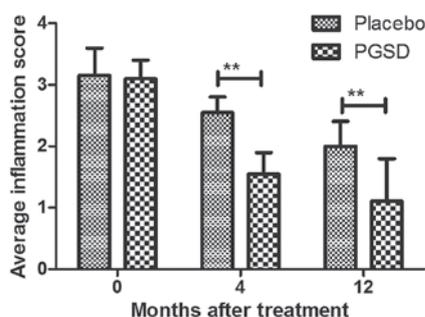


Figure 3. Average inflammation score was improved in PGSD group ( $1.1 \pm 0.7$ ) during 12-month observations. PGSD, pegaptanib sodium.

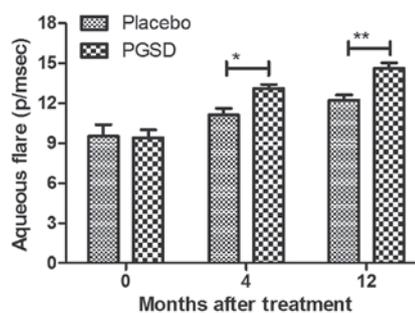


Figure 4. Intravitreal injection of PGSD treatment improves aqueous for patients with VAVR during 12-month observations. PGSD, pegaptanib sodium; VAVR, vascular active vitreoretinopathy.

pressure in patients with VAVR. Outcomes demonstrated that average inflammation score was lower in PGSD treatment group ( $1.1 \pm 0.7$ ) than in placebo ( $1.9 \pm 0.7$ ) ( $P < 0.05$ , Fig. 3) after 12-month observations. Aqueous flare examination also showed that PGSD significantly improved aqueous for patients with VAVR (Fig. 4). Intra-ocular pressure analysis showed that PGSD intravitreal injection ( $13.6 \pm 3.8$ ) improved intra-ocular pressure compared to placebo ( $10.2 \pm 4.1$  mmHg) (Fig. 5). Serum levels of inflammatory cytokines IL- $1\beta$  and TNF $\alpha$  were decreased in PGSD intravitreal injection-treated patients with VAVR (Figs. 6 and 7). We demonstrated that 12-month PGSD intravitreal injection presented enough benefits on inhibition of inflammation and improvements of intra-ocular pressure compared to placebo and 0- and 4-month PGSD treatment. These results suggest that PGSD intravitreal injection treatment plays ameliorative role in inflammation and intra-ocular pressure in patients with VAVR.

*The efficacy of PGSD intravitreal injection treatment on visual acuity and vitreoretinal traction in patients with VAVR.* The efficacy of PGSD intravitreal injection on visual acuity and vitreoretinal traction was analyzed in patients with VAVR. As shown in Fig. 8, PGSD treatment significantly improved final visual outcomes compared to placebo group. Results demonstrated mean best-corrected visual acuity significantly improved from 0.30 at baseline to 0.11 in PGSD group, while it was from 0.32 at baseline to 0.15 in placebo group. Vitreoretinal traction was improved and further meliorated retinal vasculitis for patients after treatment with PGSD intravitreal injection

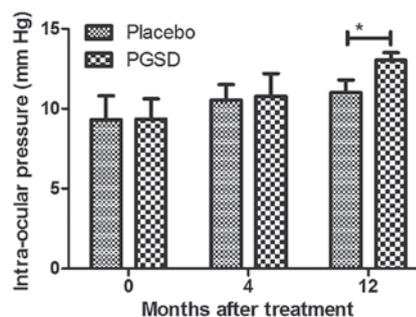


Figure 5. Intravitreal injection of PGSD treatment improves intra-ocular pressure for patients with VAVR during 12-month observations. PGSD, pegaptanib sodium.

(Figs. 9 and 10). These results suggest that 12-month PGSD intravitreal injection presented more efficacies compared to placebo and 0- and 4-month PGSD treatment on visual acuity and vitreoretinal traction in patients with VAVR.

## Discussion

Vitreoretinopathy is a serious ophthalmic disease and shows various complications of rhegmatogenous retinal detachment retinal detachment surgery (17). Despite remarkable advances in vitreoretinal surgery, VAVR still remains a common cause of severe ophthalmic complications and even visual loss (18).

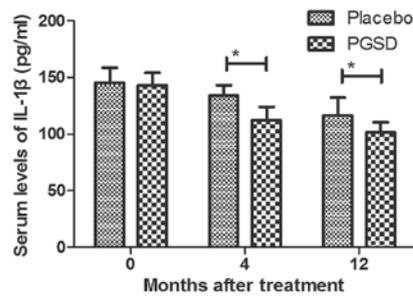


Figure 6. Intravitreal injection of PGSD treatment down-regulates serum levels of inflammatory cytokines IL-1β for patients with VAVR during 12-month observations. PGSD, pegaptanib sodium; IL-1β, interleukin 1β; VAVR, vascular active vitreoretinopathy.

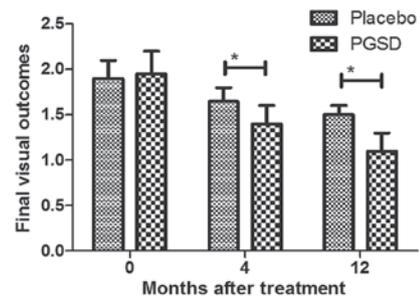


Figure 8. Intravitreal injection of PGSD treatment improves final visual outcomes compared to placebo group for patients with VAVR during 12-month observations. PGSD, pegaptanib sodium; VAVR, vascular active vitreoretinopathy.

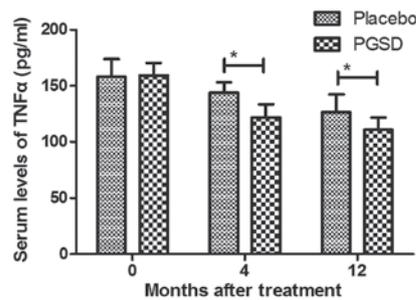


Figure 7. Intravitreal injection of PGSD treatment down-regulates serum levels of inflammatory cytokines TNFα for patients with VAVR during 12-month observations. PGSD, pegaptanib sodium; TNFα, tumor necrosis factor α; VAVR, vascular active vitreoretinopathy.

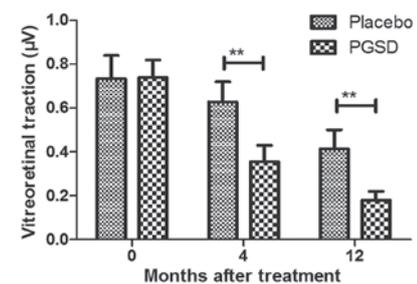


Figure 9. Vitreoretinal traction was improved by intravitreal injection of PGSD treatment compared to placebo group for patients with VAVR during 12-month observations. PGSD, pegaptanib sodium; VAVR, vascular active vitreoretinopathy.

Evidences have suggested that clinical drug nursing of PGSD treatment presents more advantages for age-related macular degeneration and vitreoretinopathy since VEGF plays essential role in the epidemiology and the symptoms of the development ophthalmic disease (19,20). The purpose of the current study systematically analyzed the role of PGSD treatment in patients with VAVR. Previous study presented that 11.2 months follow-up period of PGSD intravitreal injection significantly improved visual acuity in patients with VAVR (7). Although we observed that there were improvements a certain extent over time in patients receive 4- and 12-month treatment with placebo due to autoregulation, the efficacy of autogenous repairing is limited for patients with VAVR. Outcomes indicated that 12-month PGSD intravitreal injection markedly improved vitreoretinal traction, retinal vasculitis and visual acuity compared to placebo and 0-, 4- and 12-month treatment with PGSD for patients with VAVR.

Tractional retinal detachment induced by the formation of contractile preretinal fibrous membranes is the main reason vitreoretinopathy-induced eye syndrome or blindness (21). Results in this study indicated that PGSD intravitreal injection improves tractional retinal and intra-ocular pressure in patients with VAVR. Rinaldi, M *et al* have suggested that intravitreal PGSD (Macugen) is efficient for treatment of myopic choroidal neovascularization in a morphologic and functional study (22). Patients with VAVR receiving intravitreal injection of PGSD treatment significantly decreased subretinal exudation and leakage by fluorescein angiography compared to placebo in a 12-months follow-up. Notably, maintenance therapy with PGSD

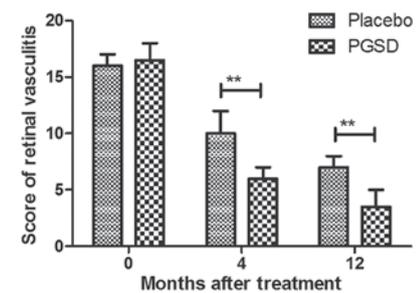


Figure 10. Intravitreal injection of PGSD treatment meliorates retinal vasculitis for patients with VAVR. PGSD, pegaptanib sodium; VAVR, vascular active vitreoretinopathy.

for nonvascular age-related macular degeneration is an effective and well-tolerated option (23). We reported that 12-month PGSD intravitreal injection markedly improved subretinal exudation and leakage compared to placebo and 0- and 4-month PGSD treatment. Report also indicated that intravitreal injection of PGSD resulted in significant clinical benefit for ocular vascular diseases by targeting of Anti-VEGF aptamer (24). Outcome showed that the pathological changes in vascular activity, amount of exudation, and visual acuity were significantly improved by intravitreal injection of PGSD treatment.

Currently, the efficacy of PGSD in improving visual acuity was identified in the 11.2-month mean follow-up period (7). In this study, we found that PGSD intravitreal injection not only improved visual acuity, but also deducted subretinal exudation and leakage in patients with VAVR. We further reported that PGSD relieved visual acuity via inhibiting

inflammatory cytokines IL-1 $\beta$  and TNF $\alpha$  for patients with VAVR. Inflammation is associated with the pathogenesis of vitreoretinopathy (25). A retrospective analysis has analyzed the safety of PGSD in the treatment of age-related macular degeneration in subjects with or without diabetes mellitus, which primarily showed the efficacy of PGSD for inflammation (26). Tikhonovich *et al* have investigated the role of inflammation in the development of proliferative vitreoretinopathy (27). Rojas *et al* have indicated that TNF $\alpha$  implicated for understanding the mechanisms of VAVR and provided evidences that increased TNF $\alpha$  may a potential new therapeutic target for Proliferative vitreoretinopathy prophylaxis (28). In addition, Keane-Myers *et al* have showed that IL-1 receptor antagonist down-modulated the recruitment of eosinophils and other inflammatory cells essential for the immunopathogenesis of ocular atopy by targeting IL-1-mediated inflammatory signal pathway (29). Our results showed that PGSD intravitreal injection treatment decreased inflammatory score and inhibited inflammatory cytokines IL-1 $\beta$  and TNF $\alpha$  for patients with VAVR. Findings demonstrated that 12-month PGSD intravitreal injection significantly inhibited inflammation and improved of intra-ocular pressure compared to placebo and 0- and 4-month PGSD treatment.

In conclusion, VAVR is still a major cause of failure of rhegmatogenous retinal detachment surgery (30-32). Intravitreal injection of PGSD treatment can improve subretinal exudation, leakage, inflammation, intra-ocular pressure, visual acuity and vitreoretinal traction for patients with VAVR, which may be a potential drug for treatment of patients with VAVR in clinic. However, further studies should be performed in a large number of populations and long-term observation in future clinic trial.

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