

Case Report

Intravitreal Tissue Plasminogen Activator Injection for Treatment-Resistant Diabetic Macular Edema of the Vitrectomized Eye

Ren Aoki Makoto Hatano Fumiaki Higashijima Takuya Yoshimoto
Masanori Mikuni Tadahiko Ogata Yuka Kobayashi Makiko Wakuta
Kazuhiro Kimura

Department of Ophthalmology, Yamaguchi University Graduate School of Medicine, Ube,
Japan

Keywords

Tissue plasminogen activator · Diabetic macular edema · Vitrectomized eye · Central retinal thickness · Visual acuity

Abstract

Diabetic macular edema (DME) is the main cause of visual loss in patients with diabetic retinopathy. DME has been treated using intravitreal anti-vascular endothelial growth factor (VEGF) drugs, steroids, laser photocoagulation, vitreoretinal surgery, and their combinations. These modalities are generally effective in preserving vision, but they sometimes produce only limited responses in patients with persistent or refractory DME. The levels of various inflammatory factors, including cytokines, chemokines, and extracellular matrices, as well as VEGF in the vitreous fluid, are increased in patients with DME. Excessive fibrinogen/fibrin levels in the vitreous fluid or fibrin deposition in the retina also contribute to DME pathogenesis. Tissue plasminogen activator (t-PA) promotes the degradation of fibrinogen or fibrin. Intravitreal t-PA injection is a commonly used treatment for subretinal hemorrhage secondary to age-related macular degeneration. Intravitreal t-PA injections have previously been used to restore vision by inducing posterior vitreous detachment in patients with DME. Herein, we describe the visual outcomes of intravitreal t-PA injection in a 78-year-old woman with treatment-resistant DME in her vitrectomized eye after several previous treatments. Before the injection, her best-corrected visual acuity (BCVA) was 0.7 logMAR and central foveal retinal thickness (CRT) was 735 μm . At 1 month after the injection, her BCVA was 0.8 logMAR and CRT was 558 μm , and 3 months later, her BCVA was 0.8 logMAR and CRT was 207 μm . Her BCVA

was sustained, and CRT showed gradual improvements. These findings suggested the effectiveness of intravitreal t-PA injections for DME in the vitrectomized eye.

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Introduction

Diabetic macular edema (DME) is one of the most common causes of vision loss in patients with diabetic retinopathy. DME occurs across all diabetic retinopathy severity levels [1]. Treatments for DME, including steroid therapy, anti-vascular endothelial growth factor (VEGF) drugs, laser therapy, and vitrectomy, effectively restore vision in many patients but sometimes produce suboptimal responses in patients with persistent or refractive DME [2]. Studies have reported that DME has a complex pathological process, including blood-retinal barrier disorders due to chronic hyperglycemia, chronic inflammation, retinal pigment epithelial disorders, oxidative stress, and increased levels of VEGF [3–5]. These factors result in the accumulation of plasma components in the stroma, including neurons and glial cells, or vitreous fluid, thereby resulting in macular thickening [4]. The levels of various inflammatory factors, including cytokines, chemokines, and extracellular matrices, as well as VEGF in the vitreous fluid increase in patients with DME [5, 6]. Excessive fibrinogen/fibrin levels in the vitreous fluid or fibrin deposition in the retina also contribute to DME pathogenesis [7, 8]. Surgical removal of the cystoid component, including fibrinogen aggregates, in the retina achieves good structural and functional outcomes in DME [9].

Tissue plasminogen activator (t-PA) is an enzyme belonging to the serine protease family; it is produced by vascular endothelial cells and plays an important role in the dissolution of blood clots [10]. In clinical ophthalmology, intravitreal t-PA injection has been found effective in DME because it induces posterior vitreous detachment [11, 12]. Studies have also reported that intravitreal t-PA injection is effective in the treatment of retinal vein occlusion and age-related macular degeneration with or without vitreous traction [13, 14].

Therefore, the effectiveness of t-PA in DME may be due to the release of vitreous traction. This is evidenced by the fact that intravitreal t-PA injection causes plasmin-induced hydrolyzation of proteins, which mediates the attachment between the posterior vitreous cortex and the retina and causes posterior vitreous detachment [11]. The tangential macular traction exerted by the posterior vitreous is one reason for macular edema, and releasing this vitreous traction improves DME; however, this concept remains controversial [15]. Herein, we report a treatment-resistant DME case of the vitrectomized eye, which could be effectively treated using intravitreal t-PA injection.

Case Report

At our hospital, we have been administering intravitreal t-PA (alteplase) injections (GRTPA 6,000,000[®]; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) for the treatment of DME under the approval of the Institutional Review Board of the Yamaguchi University School of Medicine, even though this usage is off-label. We encountered a treatment-resistant DME case of a vitrectomized eye in which intravitreal t-PA injection was effective.

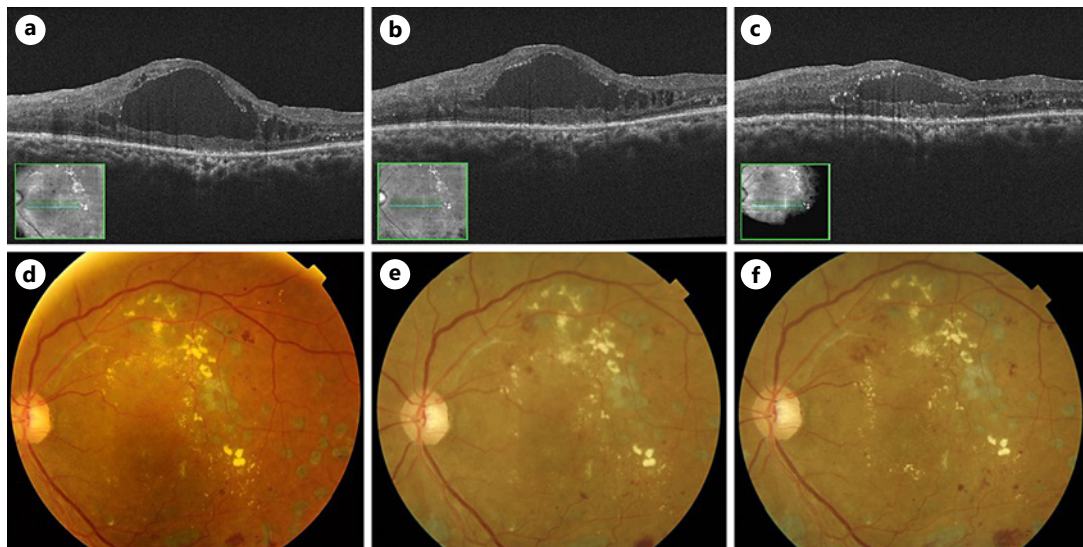


Fig. 1. OCT and color fundus photographs acquired after t-PA injection. **a** OCT image acquired before t-PA injection. **b** OCT image acquired at 1 month after t-PA injection. **c** OCT image acquired at 3 months after t-PA injection. **d** Color fundus photograph acquired before t-PA injection. **e** Color fundus photograph acquired at 1 month after t-PA injection. **f** Color fundus photograph acquired at 3 months after t-PA injection. OCT, optical coherence tomography; t-PA, tissue plasminogen activator.

A 78-year-old woman was referred to Yamaguchi University Hospital by her previous doctor for diabetic retinopathy in both eyes 6 years ago. At this time, her left eye had a best-corrected visual acuity (BCVA) of 0.3 logMAR, and the fundus findings showed petechial hemorrhages, linear hemorrhages, and hard and soft exudates. Therefore, she was diagnosed with preproliferative diabetic retinopathy and underwent pan-retinal photocoagulation. She had no other systemic diseases, except diabetes mellitus. One year after the first visit, she developed DME in the left eye and underwent 2 photocoagulations for capillary aneurysms in the macula as well as 2 sub-tenon triamcinolone acetonide injections. She had been undergoing treatment for 5 years after the onset of DME, and the treatments included 6 intravitreal triamcinolone acetonide injections, 6 intravitreal bevacizumab injections, 2 intravitreal aflibercept injections, 2 intravitreal ranibizumab injections, and one pars-plana vitrectomy with internal limiting membrane peeling. She also underwent phacoemulsification and aspiration and intraocular lens implantation, but these treatments produced no improvement in macular edema.

Thereafter, we administered intravitreal t-PA injection for the treatment-resistant DME of the vitrectomized eye. t-PA at a concentration of 15,000 IU/0.1 mL was injected into the vitreous at a point 3.5 mm from the corneal limbus. The course of treatment after intravitreal t-PA injection is shown in Figure 1. Before the t-PA injection, optical coherence tomography revealed a large cystic change in the outer plexiform layer of the fovea, and the central foveal retinal thickness (CRT) was 735 μm . The fundus findings showed an indurated hard exudate above the temporal region of the macula surrounding the macular edema. Her BCVA before the injection was 0.7 logMAR. However, no abnormal findings were noted in the anterior ocular segment and intermediate optic media. One month after the injection, the large cystic changes in the outer plexiform layer of the fovea had reduced. At this time, her CRT was 558 μm , and BCVA was 0.8 logMAR. Three months after the injection, the cystic changes in the macula had further reduced, and her CRT was 207 μm and BCVA was 0.8 logMAR. From the fundus photographs, there were no significant changes in hard exudation following treatment but a new intraretinal hemorrhage superonasal to the macula at both 1- and 3-month follow-ups.

Discussion

We present a case in which intravitreal t-PA injection in a patient with treatment-resistant DME produced favorable outcomes after standard treatment, including anti-VEGF drugs, steroids, laser photocoagulation, and vitrectomy, was unsuccessful. Although the patient's CRT improved 3 months after t-PA injection, her visual acuity remained unchanged. The changes in CRT are poorly correlated with the visual acuity outcomes. A previous study showed that the CRT changes in patients receiving anti-VEGF treatment for DME correlated with the changes in visual acuity [16]. However, other studies do not support this result. There were new intraretinal hemorrhages at 1-month and 3-month follow-ups probably because glycosylated hemoglobin, which was 7.1% before t-PA injection, worsened to 7.4% after 3 months, that is, the diabetic retinopathy itself worsened.

Intravitreal t-PA injection for DME is considered effective because it induces posterior vitreous detachment [11, 12]. Tangential vitreous traction on the macula may cause macular edema in patients with DME [17, 18]. However, in the present case, an intravitreal t-PA injection was effective in a patient without vitreous traction. Therefore, t-PA injection may have contributed to the improvement in DME through a different mechanism, other than the release of vitreous traction. The pathogenesis of macular edema in diabetic retinopathy is related to the extravascular leakage of plasma proteins such as albumin, fibrin, and fibrinogen into the retina or vitreous cavity [19]. Reports also suggest that fibrinogen is a component of the cystic changes in the macula in diabetic retinopathy [20]. Surgical removal of the cystoid component, including fibrinogen aggregates, in the retina with DME achieves good structural and functional outcomes [9]. Moreover, patients with DME have high levels of fibrinogen in the vitreous fluid, and this is adversely correlated with the recovery of visual acuity after vitrectomy [6, 21]. t-PA has a high affinity for fibrin, and it specifically adsorbs to the thrombus and converts plasminogen to plasmin on the thrombus; this plasmin breaks down fibrin and has a thrombolytic effect. Since the clinically used concentrations of t-PA have been reported to have no serious side effects on the retina in mice, and no complications have been reported in some clinical trials, intravitreal injection of t-PA is considered safe [22–24]. This case highlights the efficacy for t-PA even after vitrectomy. The case findings suggest that fibrinogen and fibrin, which are part of the cystic changes, are degraded in the retina or vitreous cavity, thereby leading to the recovery of DME.

Steroids and anti-VEGF drugs are commonly used for treating DME. The corticosteroids used in sub-tenon triamcinolone acetonide and intravitreal triamcinolone acetonide injections diminish neutrophil transmigration, limit access to the sites of inflammation, and decrease cytokine production [25–27]. They may directly inhibit growth factors such as VEGF and may have angiostatic and antipermeability properties. Anti-VEGF drugs bind to VEGF family members, such as VEGF-A, and their intravitreal levels are strongly correlated with advancing diabetic retinopathy and DME; they also decrease microvascular permeability effects and local inflammation [28]. In this case, t-PA could modulate the inflammatory process in DME through the suppression of fibrin/fibrinogen action. The estimated half-life of t-PA injected into the vitreous cavity has been reported to be 4.3–11.9 h [29]. Since t-PA is expelled from the vitreous cavity within a short time after injection, t-PA may be the first trigger to alter the equilibrium of cystic changes in the macula of diabetic retinopathy. A previous study showed that the clearance of anti-VEGF drugs in the vitreous cavity increases after vitrectomy [30]. Clearance of t-PA in vitrectomized eyes is considered more rapid than that in nonvitrectomized eyes; therefore, in this case, the effect of t-PA may have been limited.

This is a case report with a short course of 3 months. Future studies of multiple cases with long-term follow-up are needed.

Conclusion

In conclusion, we administered intravitreal t-PA injection for treatment-resistant DME in vitrectomized eyes and found a significant improvement in CRT after 3 months. This result suggests that intravitreal t-PA injection might have therapeutic implications for DME in vitrectomized eyes. In the future, we hope to assess more cases of this condition and perform a long-term follow-up to determine the beneficial effects of this potentially novel treatment modality for patients with treatment-resistant DME.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. All procedures contributing to this work were reviewed and approved by the Yamaguchi University Hospital Institutional Review Board (APPROVAL reference number: H29-092) and adhered to the tenets of the Helsinki Declaration.

Conflict of Interest Statement

The authors report no conflicts of interest in this work.

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Author Contributions

Ren Aoki designed the study and wrote the initial draft of the manuscript. Kazuhiro Kimura was the corresponding author, contributed to the analysis and interpretation of data, and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation and critically reviewed the manuscript. All the authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

- 1 Duh EJ, Sun JK, Stitt AW. Diabetic retinopathy: current understanding, mechanisms, and treatment strategies. *JCI Insight*. 2017 Jul 20;2(14):e93751.
- 2 Terasaki H, Ogura Y, Kitano S, Sakamoto T, Murata T, Hirakata A, et al. Management of diabetic macular edema in Japan: a review and expert opinion. *Jpn J Ophthalmol*. 2018 Jan;62(1):1–23.
- 3 Uji A, Murakami T, Unoki N, Ogino K, Horii T, Yoshitake S, et al. Parallelism for quantitative image analysis of photoreceptor-retinal pigment epithelium complex alterations in diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2014 May 8;55(5):3361–7.
- 4 Zhang X, Zeng H, Bao S, Wang N, Gillies MC. Diabetic macular edema: new concepts in patho-physiology and treatment. *Cell Biosci*. 2014;4:27.
- 5 Cacciamani A, Esposito G, Scarinci F, Parravano M, Dinice L, Di Nicola M, et al. Inflammatory mediators in the vitreal reflux of patients with diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol*. 2019 Jan;257(1):187–97.
- 6 Kimura K, Orita T, Kobayashi Y, Matsuyama S, Fujimoto K, Yamauchi K. Concentration of acute phase factors in vitreous fluid in diabetic macular edema. *Jpn J Ophthalmol*. 2017 Nov;61(6):479–83.
- 7 Murata T, Ishibashi T, Inomata H. Immunohistochemical detection of extravasated fibrinogen (fibrin) in human diabetic retina. *Graefes Arch Clin Exp Ophthalmol*. 1992;230(5):428–31.
- 8 Wei Q, Zhang T, Jiang R, Chang Q, Zhang Y, Huang X, et al. Vitreous fibronectin and fibrinogen expression increased in eyes with proliferative diabetic retinopathy after intravitreal anti-VEGF therapy. *Invest Ophthalmol Vis Sci*. 2017 Nov 1;58(13):5783–91.
- 9 Imai H, Otsuka K, Tetsumoto A, Miki A, Nakamura M. Effectiveness of en bloc removal of fibrinogen-rich component of cystoid lesion for the treatment of cystoid macular edema. *Retina*. 2020 Jan;40(1):154–9.
- 10 Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood Rev*. 2015 Jan;29(1):17–24.
- 11 Hesse L, Nebeling B, Schroeder B, Heller G, Kroll P. Induction of posterior vitreous detachment in rabbits by intravitreal injection of tissue plasminogen activator following cryopexy. *Exp Eye Res*. 2000 Jan;70(1):31–9.
- 12 Abrishami M, Moosavi MN, Shoeibi N, Hosseinpour SS. Intravitreal tissue plasminogen activator to treat refractory diabetic macular edema by induction of posterior vitreous detachment. *Retina*. 2011 Nov;31(10):2065–70.
- 13 Murakami T, Takagi H, Kita M, Nishiwaki H, Miyamoto K, Ohashi H, et al. Intravitreal tissue plasminogen activator to treat macular edema associated with branch retinal vein occlusion. *Am J Ophthalmol*. 2006 Aug;142(2):318–20.
- 14 Kachi I, Yasukawa T, Kato A, Takase N, Morita H, Kubota A, et al. Combination therapy with intravitreal tissue plasminogen activator and ranibizumab for subfoveal type 2 choroidal neovascularization. *Jpn J Ophthalmol*. 2016 May;60(3):179–86.
- 15 Kaiser PK, Riemann CD, Sears JE, Lewis H. Macular traction detachment and diabetic macular edema associated with posterior hyaloidal traction. *Am J Ophthalmol*. 2001 Jan;131(1):44–9.
- 16 Bressler NM, Odia I, Maguire M, Glassman AR, Jampol LM, MacCumber MW, et al. Association between change in visual acuity and change in central subfield thickness during treatment of diabetic macular edema in participants randomized to aflibercept, bevacizumab, or ranibizumab: a post hoc analysis of the protocol T randomized clinical trial. *JAMA Ophthalmol*. 2019;137(9):977–85.
- 17 Stefanitou M, Aspiotis M, Kalogeropoulos C, Christodoulou A, Psylla M, Ioachim E, et al. Vitrectomy results for diffuse diabetic macular edema with and without inner limiting membrane removal. *Eur J Ophthalmol*. 2004 Mar–Apr;14(2):137–43.
- 18 Stolba U, Binder S, Gruber D, Krebs I, Aggermann T, Neumaier B. Vitrectomy for persistent diffuse diabetic macular edema. *Am J Ophthalmol*. 2005 Aug;140(2):295–301.
- 19 Haller JA, Haller JA, Qin H, Apte RS, Beck RR, Bressler NM, et al., Diabetic Retinopathy Clinical Research Network Writing Committee. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. *Ophthalmology*. 2010 Jun;117(6):1087–93.e3.
- 20 Terada N, Murakami T, Uji A, Dodo Y, Mori Y, Tsujikawa A. Hyperreflective walls in foveal cystoid spaces as a biomarker of diabetic macular edema refractory to anti-VEGF treatment. *Sci Rep*. 2020 Apr 29;10(1):7299.
- 21 Kralinger MT, Pedri M, Kralinger F, Troger J, Kieselbach GF. Long-term outcome after vitrectomy for diabetic macular edema. *Ophthalmologica*. 2006;220(3):147–52.
- 22 Elman MJ, Raden RZ, Carrigan A. Intravitreal injection of tissue plasminogen activator for central retinal vein occlusion. *Trans Am Ophthalmol Soc*. 2001;99:219–3; discussion 22–3.
- 23 Tagami M, Kusahara S, Imai H, Honda S, Tsukahara Y, Negi A. Impact of intravitreal injection of tissue plasminogen activator on full-field electroretinogram in patients with macular oedema secondary to retinal vein occlusion. *Ophthalmologica*. 2011;226(2):81–6.
- 24 Ozone D, Mizutani T, Nozaki M, Ohbayashi M, Hasegawa N, Kato A, et al. Tissue plasminogen activator as an antiangiogenic agent in experimental laser-induced choroidal neovascularization in mice. *Invest Ophthalmol Vis Sci*. 2016;57(13):5348–54.
- 25 Ciulla TA, Walker JD, Fong DS, Criswell MH. Corticosteroids in posterior segment disease: an update on new delivery systems and new indications. *Curr Opin Ophthalmol*. 2004 Jun;15(3):211–20.
- 26 Edelman JL, Lutz D, Castro MR. Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. *Exp Eye Res*. 2005 Feb;80(2):249–58.

- 27 Campochiaro PA, Hafiz G, Mir TA, Scott AW, Zimmer-Galler I, Shah SM, et al. Pro-permeability factors in diabetic macular edema; the diabetic macular edema treated with ozurdex trial. [Am J Ophthalmol](#). 2016 Aug; 168:13–23.
- 28 Krick TW, Bressler NM. Recent clinically relevant highlights from the diabetic retinopathy clinical research network. [Curr Opin Ophthalmol](#). 2018 May;29(3):199–205.
- 29 Jaffe GJ, Green GD, McKay BS, Hartz A, Williams GA. Intravitreal clearance of tissue plasminogen activator in the rabbit. [Arch Ophthalmol](#). 1988 Jul;106(7):969–72.
- 30 Edington M, Connolly J, Chong NV. Pharmacokinetics of intravitreal anti-VEGF drugs in vitrectomized versus non-vitrectomized eyes. [Expert Opin Drug Metab Toxicol](#). 2017 Dec;13(12):1217–24.