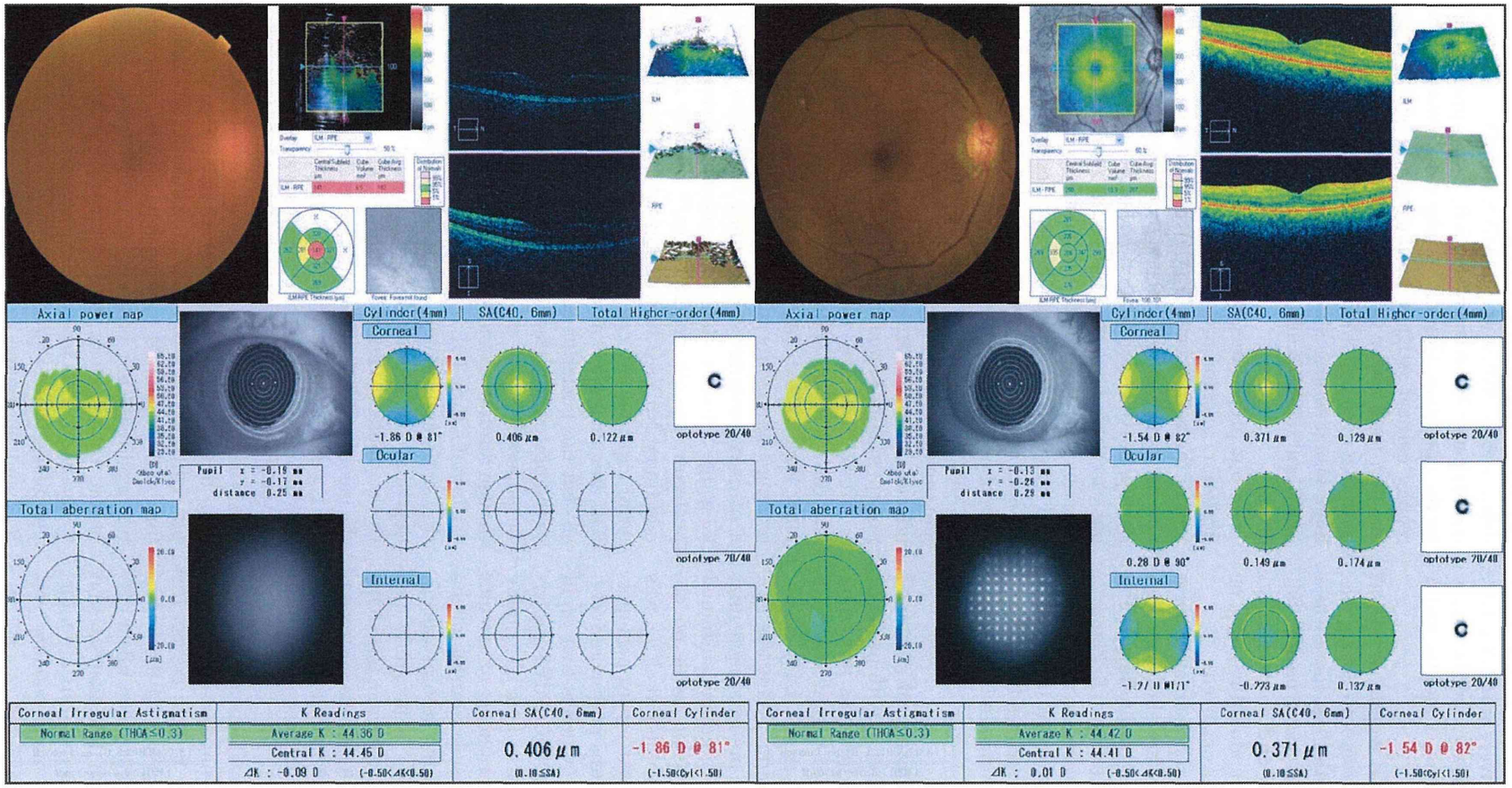

Figure 4. Representative eye (Patient 12 in Table 1) with proliferative diabetic retinopathy (PDR) (Patient 12; see Table 1). Preoperative and postoperative findings of the eye of a 66-year-old woman with PDR. The eye had undergone combined 25-gauge microincision vitrectomy surgery (25G MIVS) and toric IOL implantation with posterior capsulotomy. (Upper left) Preoperative photograph of the right fundus and findings of optical coherent tomography showing vitreous hemorrhage (VH) and low signal intensity due to VH, respectively. (Upper right) Postoperative photograph of the right fundus and findings of optical coherent tomography showing no VH and good foveal centralis, respectively. (Lower left) Preoperative findings of a wavefront analyzer showing cylindrical against-the-rule corneal astigmatism. The internal and ocular total astigmatism could not be detected due to VH. Preoperatively, logMAR uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) in this eye were 1.40 and 1.15, respectively. (Lower right) Postoperative findings of a wave-front analyzer showing cylindrical against-the-rule corneal astigmatism, unchanged from the preoperative condition. Internal and ocular total astigmatism could be detected because VH had been successfully removed by the 25G MIVS procedure. The ocular total cylindrical astigmatism was almost completely corrected postoperatively because the internal cylindrical astigmatism (toric IOL) had a strong corrective effect on the corneal astigmatism. Postoperatively, logMaAR UCVA and BCVA in this eye were both –0.08.

lems visualizing the peripheral lesion. However, the wide-viewing system should eliminate any trouble visualizing the macular and peripheral regions, because the system can theoretically visualize all retinal lesions solely through the small central region of the toric IOL. This region has little corrective effect on astigmatism, and the possibility of visual distortion for the surgeon is thus minimal. In fact, we used the wide-viewing system to perform peripheral vitrectomy and panretinal endolaser photocoagulation for the PDR eye (Patient 12 in Table 1; Figure 1, upper right) without difficulty. Thus, we recommend that a toric IOL should be inserted in the first half of the combined surgery (before vitrectomy), following which 25G MIVS should be performed through a conventional contact lens for the macular region and through the wide-viewing system for the peripheral region.

The reason why the toric IOL should be inserted in the first half of the combined surgery is to confirm its rotational stability. If the toric IOL were inserted at the end of the vitrectomy, the rotational stability of the toric IOL could not be completely confirmed intraoperatively. Vitreous surgeons need to confirm the stability of the toric IOL intraoperatively because of the chance that the implanted toric IOL could be unstable at an early phase after its insertion. However, we believe that in our cases, the toric IOL with posterior capsulotomy was stably positioned several minutes after insertion. We have previously reported the difficulty of seeing through the implanted IOL with posterior capsulotomy in cases in which fluid-air exchange is used.[27] This is because the retro-surface of the IOL can have an irregular reflex, or there can be dew in the fluid-air exchange. Therefore, in cases with retinal detachment that are expected to require intraoperative fluid-air exchange, phacovitrectomy with a toric IOL and posterior capsulotomy should be performed with caution.

If postoperative iris synechiae occur, the implanted toric IOL can be affected and become tilted. Therefore, it might be advisable to avoid our procedure in cases such as severe PDR, proliferative vitreoretinopathy (PVR), or uveitis, because they require lengthy surgery to treat the proliferative tissue and an injection of perfluoropropane.[31] However, we believe that under favorable conditions in the anterior and posterior segments, our technique is the best approach to treating retinal diseases with corneal astigmatism to achieve the highest quality of postoperative vision. Thus, preoperative examination of lenticular and retinal conditions is very important when considering 25G MIVS and toric IOL implantation with posterior capsulotomy.

The limitations of our study include its retrospective nature, small patient population, and short follow-up period. In addition, retinal diseases with corneal astigmatism can be accompanied by severe PDR, PVR, weak zonules, or pseudoexfoliation syndrome. Retinal conditions such as longstanding macula-off PDR or PVR would not be suitable for implanting a toric IOL using this technique, because the postoperative visual prognosis would be poor. Anterior conditions such as weak zonules or pseudoexfoliation syndrome would also contraindicate implanting a toric IOL using this technique because of the postoperative instability of the capsular bag.

In conclusion, it is possible to fix a toric IOL with posterior capsulotomy during 25G MIVS. This procedure is a practical and safe approach in eyes with concurrent vitreoretinal disease and corneal astigmatism. The pre-existing regular corneal cylinder is corrected efficiently and stably, and the improvement in postoperative vision is rapid and sustained, with no occurrence of PCO. Further investigation toward establishing this procedure as standard is merited. Taking corneal astigmatism into consideration when patients with retinal disease require surgical intervention may result in higher postoperative visual function.

REFERENCES

1. Galway G, Drury B, Cronin BG, Bourke RD. A comparison of induced astigmatism in 20- vs 25-gauge vitrectomy procedures. *Eye (Lond).* 2010;24(2):315-317.
2. Avitabile T, Castiglione F, Bonfiglio V. Transconjunctival sutureless 25-gauge versus 20-gauge standard vitrectomy: correlation between corneal topography and ultrasound biomicroscopy measurements of sclerotomy sites. *Cornea.* 2010;29(1):19-25.
3. Shinoda H, Shinoda K, Satofuka S, et al. Visual recovery after vitrectomy for macular hole using 25-gauge instruments. *Acta Ophthalmol.* 2008;86(2):151-155.
4. Valmaggia C. Pars plana vitrectomy with 25-gauge instruments in the treatment of idiopathic epiretinal membranes. *Klin Monbl Augenheilkd.* 2007;224(4):292-296.
5. Okamoto F, Okamoto C, Sakata N, et al. Changes in corneal topography after 25-gauge transconjunctival sutureless vitrectomy versus after 20-gauge standard vitrectomy. *Ophthalmology.* 2007;114(12):2138-2141.
6. Kadonosono K, Yamakawa T, Uchio E, et al. Comparison of visual function after epiretinal membrane removal by 20-gauge and 25-gauge vitrectomy. *Am J Ophthalmol.* 2006;142(3):513-515.
7. Yanyali A, Celik E, Horozoglu F, Nohutcu AF. Corneal topographic changes after transconjunctival (25-gauge) sutureless vitrectomy. *Am J Ophthalmol.* 2005;140(5):939-941.
8. Mendicute J, Irigoyen C, Aramberri J, Ondarra A, Montés-Micó R. Foldable toric intraocular lens for astigmatism correction in cataract patients. *J Cataract Refract Surg.* 2008;34(4):601-607.
9. Till JS, Yoder PR Jr., Wilcox TK, Spielman JL. Toric intraocular lens implantation: 100 consecutive cases. *J Cataract Refract Surg.* 2002;28(2):295-301.
10. Ruhswurm I, Scholz U, Zehetmayer M, Hanselmayer G, Vass C, Skorpik C. Astigmatism correction with a foldable toric intraocular lens in cataract patients. *J Cataract Refract Surg.* 2000;26(7):1022-1027.
11. Ferrer-Blasco T, Montés-Micó R, Peixoto-de-Matos SC, González-

Méijome JM, Cerviño A. Prevalence of corneal astigmatism before cataract surgery. *J Cataract Refract Surg.* 2009;35(1):70-75.
12. Fujii GY, De Juan E, Jr., Humayun MS, et al. A new 25-gauge instrument system for transconjunctival sutureless vitrectomy surgery. *Ophthalmology.* 2002;109(10):1807-1812.
13. Fujii GY, De Juan E, Jr., Humayun MS, et al. Initial experience using the transconjunctival sutureless vitrectomy system for vitreoretinal surgery. *Ophthalmology.* 2002;109(10):1814-1820.
14. Kunikata H, Nitta F, Meguro Y, et al. Difficulty in inserting 25- and 23-gauge trocar cannula during vitrectomy. *Ophthalmologica.* 2011;226(4):198-204.
15. Shimada H, Nakashizuka H, Mori R, Mizutani Y. Expanded indications for 25-gauge transconjunctival vitrectomy. *Jpn J Ophthalmol.* 2005;49(5):397-401.
16. Gonzales CR, Boshra J, Schwartz SD. 25-Gauge pars plicata vitrectomy for stage 4 and 5 retinopathy of prematurity. *Retina.* 2006;26(7 Suppl):S42-6.
17. Riemann CD, Miller DM, Foster RE, Petersen MR. Outcomes of transconjunctival sutureless 25-gauge vitrectomy with silicone oil infusion. *Retina.* 2007;27(3):296-303.
18. Kadonosono K, Yamakawa T, Uchio E, et al. Fibrovascular membrane removal using a high-performance 25-gauge vitreous cutter. *Retina.* 2008;28(10):1533-1535.
19. Kiss S, Vavvas D. 25-gauge transconjunctival sutureless pars plana vitrectomy for the removal of retained lens fragments and intraocular foreign bodies. *Retina.* 2008;28(9):1346-1351.
20. Lai MM, Ruby AJ, Sarrafizadeh R, et al. Repair of primary rhegmatogenous retinal detachment using 25-gauge transconjunctival sutureless vitrectomy. *Retina.* 2008;28(5):729-734.
21. Kunikata H, Nishida K. Visual outcome and complications of 25-gauge vitrectomy for rhegmatogenous retinal detachment: 84 consecutive cases. *Eye (Lond).* 2010;24(6):1071-1077.
22. Farouk MM, Naito T, Sayed KM, et al. Outcomes of 25-gauge vitrectomy for proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol.* 2011;249(3):369-376.
23. Kunikata H, Abe T, Nishida K. Successful outcomes of 25- and 23-gauge vitrectomies for giant retinal tear detachments. *Ophthalmic Surg Lasers Imaging.* 2011;42(6):487-492.
24. Kunikata H, Fuse N, Abe T. Fixating dislocated intraocular lens by 25-gauge vitrectomy. *Ophthalmic Surg Lasers Imaging.* 2011;42(4):297-301.
25. Kunikata H, Uematsu M, Nakazawa T, Fuse N. Successful removal of large intraocular foreign body by 25-gauge microincision vitrectomy surgery. *J Ophthalmol.* 2011;2011:940323.
26. Sato S, Inoue M, Kobayashi S, Watanabe Y, Kadonosono K. Primary posterior capsulotomy using a 25-gauge vitreous cutter in vitrectomy combined with cataract surgery. *J Cataract Refract Surg.* 2010;36(1):2-5.
27. Aizawa N, Kunikata H, Abe T, Nakazawa T. Efficacy of combined 25-gauge microincision vitrectomy, intraocular lens implantation, and posterior capsulotomy. *J Cataract Refract Surg.* 2012;38(9):1602-1607.
28. Shimada H, Nakashizuka H, Mori R, Mizutani Y, Hattori T. 25-gauge scleral tunnel transconjunctival vitrectomy. *Am J Ophthalmol.* 2006;142(5):871-873.
29. Mingo-Botín D, Muñoz-Negrete FJ, Won Kim HR, Morcillo-Laiz R, Rebolleda G, Oblanca N. Comparison of toric intraocular lenses and peripheral corneal relaxing incisions to treat astigmatism during cataract surgery. *J Cataract Refract Surg.* 2010;36(10):1700-1708.
30. Koshy JJ, Nishi Y, Hirnschall N, et al. Rotational stability of a single-piece toric acrylic intraocular lens. *J Cataract Refract Surg.* 2010;36(10):1665-1670.
31. Kim SW, Oh J, Song JS, Kim YY, Oh IK, Huh K. Risk factors of iris posterior synechia formation after phacovitrectomy with three-piece acrylic IOL or single-piece acrylic IOL. *Ophthalmologica.* 2009;223(4):222-227.

Intraocular Concentrations of Cytokines and Chemokines in Rhegmatogenous Retinal Detachment and the Effect of Intravitreal Triamcinolone Acetonide

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• PURPOSE: To investigate the role of intravitreal injection of triamcinolone acetonide (IVTA) in preventing photoreceptor apoptosis in eyes with rhegmatogenous retinal detachment (RRD) by measuring cytokine levels in the aqueous humor before and after IVTA.

• DESIGN: Prospective, nonrandomized, interventional case series.

• METHODS: SETTING: Institutional. PATIENTS: Nineteen eyes of 19 consecutive patients with RRD. INTERVENTION: All 19 eyes underwent IVTA 1 day before 25-gauge vitrectomy. Seventeen eyes free of retinal vascular disease served as controls. MAIN OUTCOME MEASURE: Both baseline and 1 day post-IVTA measurements were made of the relative concentrations of 15 soluble factors (3 cytokines, 7 chemokines, and 5 growth factors). The associations with clinical findings, including macular status, were then analyzed.

• RESULTS: Elevated monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1β (MIP-1β), and interferon γ–induced protein 10 (IP-10) in eyes with RRD were significantly reduced after IVTA. MCP-1 levels were significantly correlated with MIP-1β and IP-10 before and after IVTA. The decreases in MCP-1, MIP-1β, and IP-10 were also closely correlated to each other. Both before and after IVTA, MCP-1 was higher in eyes with macula-off RRD than in eyes with macula-on RRD.

• CONCLUSIONS: IVTA suppressed elevated levels of intraocular MCP-1, MIP-1β, and IP-10 in eyes with RRD. The decrease in the aqueous levels of each of these factors was significantly correlated with the others. In addition to MCP-1, MIP-1β and IP-10 might potentially be additional target molecules for RRD therapy. (Am J Ophthalmol 2013;155:1028–1037. © 2013 by Elsevier Inc. All rights reserved.)

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RHEGMATOGENOUS RETINAL DETACHMENT (RRD) IS a common retinal disease that causes visual field defects and severe visual disturbance. Newly developed surgical interventions, particularly 25-gauge microincision vitrectomy surgery (25GMIVS), have led to a very high initial reattachment rate for eyes with RRD, currently about 95%.[1–10] Even after successful reattachment, however, degeneration of the photoreceptors in the detached area of the retina often prevents complete recovery of visual function.[1,11]

Vitreous samples from eyes with RRD have shown significantly elevated levels of monocyte chemotactic protein 1 (MCP-1) compared to controls.[12,13] Previous research by our team, performed with an experimental animal model, showed that MCP-1, along with tumor necrosis factor α (TNF-α), is implicated in the pathogenesis of photoreceptor degeneration and apoptosis following retinal detachment.[14–16] Furthermore, the administration of antibodies and corticosteroid suppressed photoreceptor degeneration and apoptosis in our animal model and lowered the intraocular expression of both MCP-1 and TNF-α. The current study examines the specific effects of corticosteroid in human subjects with RRD. Corticosteroid is already in wide use for a variety of ocular diseases, and triamcinolone acetonide (TA) in particular is well recognized for its anti-inflammatory properties. There are many reports on the successful use of intravitreal injection of triamcinolone acetonide (IVTA) as a treatment for exudative conditions of the posterior segment.[17–25]

In this prospective study, therefore, we hypothesized that in the preoperative period, IVTA would suppress inflammation and photoreceptor apoptosis in human eyes with RRD. To evaluate our hypothesis, we measured levels of intraocular mediators including chemokines and cytokines, such as MCP-1 and TNF-α, and analyzed their response to IVTA in eyes with RRD. Thus, the purpose of this report is to evaluate the effect of IVTA on the intraocular concentration of mediators in eyes with RRD.

MATERIALS AND METHODS

• SETTING AND DESIGN: This was an institutional, prospective, nonrandomized, interventional case series.

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TABLE. Aqueous Humor Levels of the Inflammatory Mediators Before and After Intravitreal Injection of Triamcinolone Acetonide

Groups	Mediators	Control (n = 17) (pg/mL)	RRD (n = 19)		*P* Value	
			Baseline (pg/mL)	After IVTA (pg/mL)	C vs B	B vs I
Cytokines	IL-6	21 ± 23	261 ± 674	277 ± 617	<.001[a]	.27
	IFN-γ	5.4 ± 8.2	16.8 ± 12.7	22.9 ± 9.6	.003[a]	.04[b]
	TNF-α	4.0 ± 7.3	3.6 ± 2.9	4.9 ± 2.8	.02[a]	.02[b]
Chemokines	MCP-1	177 ± 26	1004 ± 667	591 ± 515	<.001[a]	<.001[b]
	MIP-1α	1.3 ± 2.9	0.14 ± 0.28	0.22 ± 0.28	.77	.21
	MIP-1β	11 ± 3.7	33.4 ± 16.7	22.2 ± 10.3	<.001[a]	.004[b]
	RANTES	2.8 ± 3.4	3.0 ± 2.4	5.9 ± 3.2	.48	.008[b]
	Eotaxin	0.0 ± 0.0	22.6 ± 18.7	35.0 ± 21.0	<.001[a]	.11
	IP-10	485 ± 491	2384 ± 2553	1936 ± 1856	<.001[a]	.04[b]
	IL-8	4.5 ± 2.9	21.6 ± 11.6	26.7 ± 16.8	<.001[a]	.20
Growth factors	VEGF	61 ± 25	123 ± 67	206 ± 117	.003[a]	<.001[b]
	bFGF	9.5 ± 8.8	11.9 ± 11.5	20.3 ± 11.5	.35	.009[b]
	G-CSF	1.9 ± 3.4	19.7 ± 38.9	97.2 ± 107.8	<.001[a]	<.001[b]
	GM-CSF	191 ± 37	212 ± 68	275 ± 59	.23	.001[b]
	PDGF-BB	3.8 ± 5.3	5.3 ± 3.9	9.4 ± 4.1	.06	.007[b]

B = RRD at baseline; bFGF = basic fibroblast growth factor; C = control; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; I = RRD after IVTA; IFN-γ = interferon γ; IL-6 = interleukin 6; IL-8 = interleukin 8; IP-10 = interferon gamma–induced protein 10; IVTA =intravitreral injection of triamcinolone acetonide; MCP-1 = monocyte chemotactic protein 1; MIP-1α = macrophage inflammatory protein 1α; MIP-1β = macrophage inflammatory protein 1β; PDGF-BB = platelet-derived growth factor BB; RANTES = regulated on activation, normal T cell expressed and secreted; RRD = rhegmatogenous retinal detachment; TNF-α = tumor necrosis factor α; VEGF = vascular endothelial growth factor.

[a]Mann-Whitney *U* test.

[b]Wilcoxon signed rank test.

Subjects were recruited from patients referred to the Surgical Retina Service of Tohoku University Hospital. Surgical intervention and follow-up were both performed at this clinic. Informed consent for both the treatment and participation in the research for this prospective study (University Hospital Medical Information Network; UMIN Study ID N.: UMIN000009418) was approved by the institutional review board of Tohoku University Graduate School of Medicine (Prot. N.2006-262, November 20, 2006). Informed consent for both the treatment and participation in the research was obtained from each patient and the research was conducted according to the provisions of the Declaration of Helsinki, 1995 (as revised in Edinburgh, 2000).

• PATIENTS: All patients had RRD and were studied in the period before 25GMIVS. The inclusion criterion was clinically detectable RRD. The exclusion criteria were prior vitreous surgery or IVTA, intravitreal anti–vascular endothelial growth factor (VEGF), ocular inflammation, and vitreoretinal or optic nerve diseases. Clinical and demographic characteristics were collected, including age, macular status, extent of RRD, number of retinal breaks, preoperative best-corrected visual acuity (BCVA), 1-month-postoperative BCVA, 6-month-postoperative BCVA, 1-month-postoperative foveal thickness (FT), and 6-month-postoperative FT. BCVA was measured with the Landolt C visual acuity chart, and the decimal acuities were converted to logarithms of the minimal angle of resolution (logMAR) units. The extent of the RRD was graded 1 to 4 according to the number of quadrants it covered.

• INTERVENTION: IVTA was performed in all patients 1 day before 25GMIVS. The TA (Kenacort-A; Bristol-Meyers Squibb, Tokyo, Japan) diluent was replaced with a balanced salt solution (BSS Plus; Alcon Laboratories, Fort Worth, Texas, USA) after Millipore filtration (Millex GS Filter Unit with MF-Millipore MCE Membrane, 0.22 μm; Merck Millipore Ltd., Tullagreen, Carrigtwohill, County Cork, Ireland), and the volume was adjusted so that 0.1 mL contained 4 mg TA. The TA was injected using a 27-gauge needle and a standard pars plana approach (3.5 mm posterior to the limbus). Before performing IVTA, samples of the aqueous humor were collected and the levels of mediators in the anterior chamber were measured. We next performed IVTA, and a day later collected a second aqueous humor sample, before beginning 25GMIVS. During 25GMIVS, we also collected samples of the vitreous. Patients undergoing 25GMIVS for epiretinal membrane (ERM) or macular hole (MH) served as controls.

• MAIN OUTCOME MEASURE: We investigated mediator levels in the pre- and post-IVTA aqueous humor, as well as the relationship between mediator levels and clinical findings

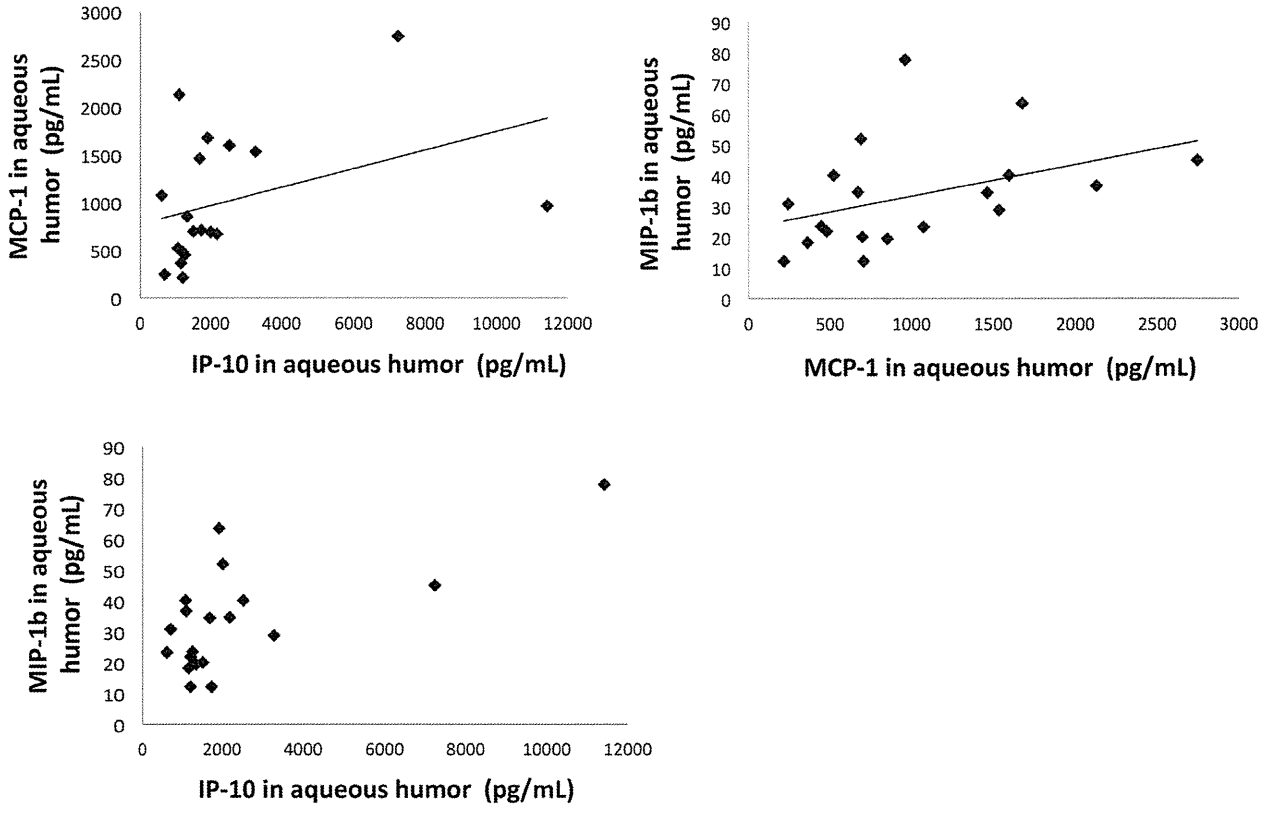

FIGURE 1. Relationship between chemokine levels in the aqueous humor before intravitreal injection of triamcinolone acetonide. (Top left) The aqueous humor level of monocyte chemotactic protein 1 (MCP-1) was significantly correlated with that of interferon γ–induced protein 10 (IP-10) ($r = 0.48$, $P = .04$). (Top right) In addition, the aqueous humor level of MCP-1 was significantly correlated with that of macrophage inflammatory protein 1β (MIP-1β) ($r = 0.50$, $P = .03$). (Bottom) The aqueous humor level of IP-10 was likely correlated with that of MIP-1β, but not significantly ($r = 0.44$, $P = .06$).

including age, macular status, size of RRD, number of retinal tears, preoperative BCVA, 1-month-postoperative BCVA, 6-month-postoperative BCVA, 1-month-postoperative FT, and 6-month-postoperative FT. We also measured mediator levels in the post-IVTA vitreous.

• MEASUREMENT OF INFLAMMATORY MEDIATORS: We withdrew aqueous humor samples before IVTA with a 30-gauge needle, to prevent increasing intraocular pressure later on, after IVTA. We next collected aqueous humor samples 1 day after IVTA, just before 25GMIVS. Special care was taken to avoid touching intraocular tissues (ie, the cornea, the iris, and the lens) and to prevent mixing intraocular samples with other fluids. The samples of aqueous humor (about 100 μL) were collected in sterile tubes and were immediately frozen at −80 C. Control samples of the aqueous humor from eyes undergoing vitreous surgery for ERM or MH were collected as controls and were also immediately frozen. The inflammatory mediators we investigated fell into 3 groups: (1) 3 cytokines: interleukin 6 (IL-6), interferon γ (IFN-γ), and TNF-α; (2) 7 chemokines: MCP-1/CCL2; macrophage inflammatory protein 1α (MIP-1α)/CCL3; macrophage inflammatory protein 1β (MIP-1β)/CCL4; regulated on activation, normal T cell expressed and secreted (RANTES)/CCL5; eotaxin/CCL11; interferon γ–induced protein 10 (IP-10)/CXCL10; and IL-8/CXCL8; and (3) 5 growth factors: VEGF, basic fibroblast growth factor (bFGF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and platelet-derived growth factor BB (PDGF-BB). Samples were analyzed using a multiplex bead analysis system, the Bio-Plex system (Bio-Rad Laboratories, Hercules, California, USA). A custom-made kit (Bio-Plex Human Cytokine Assay; Bio-Rad Laboratories) was used to detect the mediators. For the experiment, aqueous humor and vitreous samples were diluted 4 times with sample diluent (Bio-Rad Laboratories). A total volume of 50 μL from each sample was used for the assay. The kits were used according to the manufacturer's instructions.

• STATISTICAL ANALYSES: All analyses were performed with Ekuseru-Toukei 2006 software (Social Survey Research Information Co Ltd, Tokyo, Japan). The data

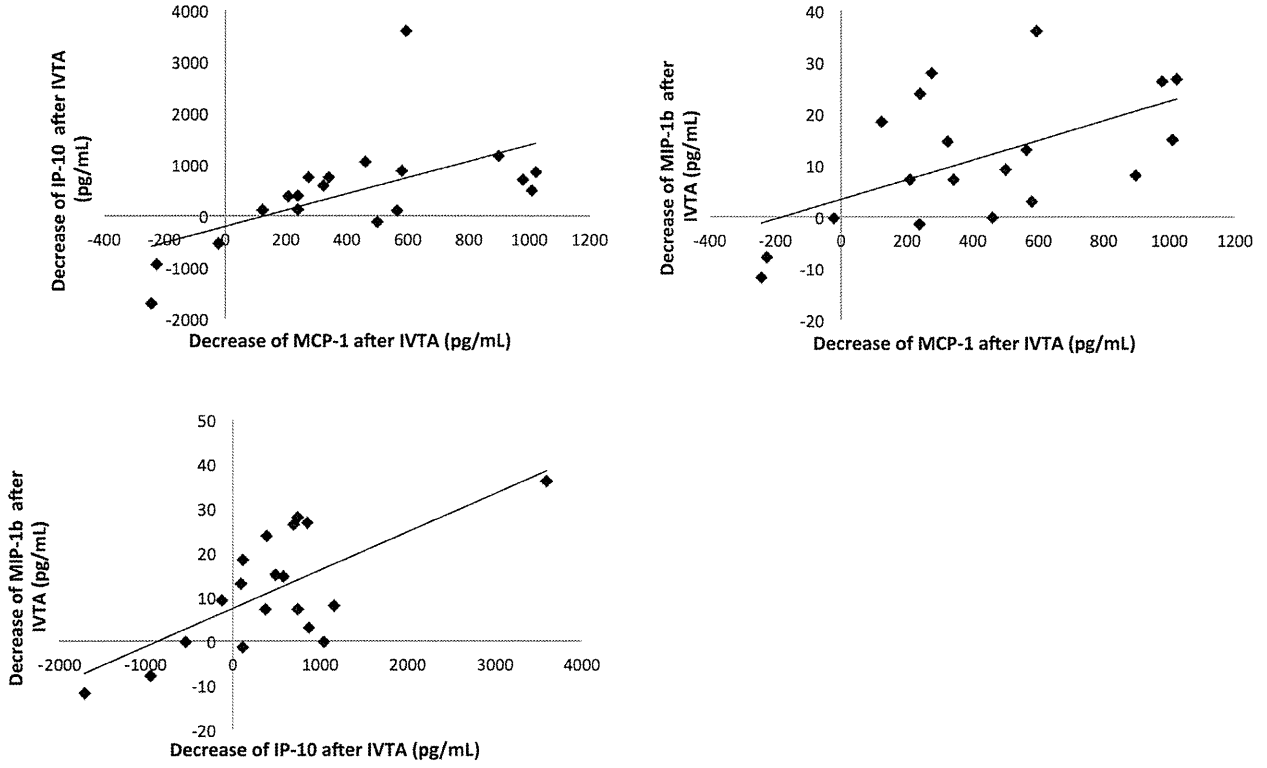

FIGURE 2. Alterations of levels of chemokines in the aqueous humor after intravitreal injection of triamcinolone acetonide. After intravitreal injection of triamcinolone acetonide (IVTA), the aqueous humor levels of monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1β (MIP-1β), and interferon γ–induced protein 10 (IP-10) were significantly reduced ($P < .001$, $P = .004$, and $P = .04$, respectively). Each mediator showed a correlated decrease with the others (Top left: MCP-1 and IP-10: $r = 0.69$, $P = .001$; Top right: MCP-1 and MIP-1β: $r = 0.57$, $P = .01$; Bottom: IP-10 and MIP-1β: $r = 0.47$, $P = .04$).

are presented as means ± standard deviation. The significance of the difference between the pre- and post-IVTA data was assessed by the Wilcoxon signed rank test. The significance of the difference in the concentration of cytokines between eyes with an RRD and control subjects was assessed by the Mann-Whitney *U* test. The Spearman coefficient of correlation by rank was calculated to determine the correlation between aqueous humor and vitreous levels of the mediators. The Spearman coefficient of correlation by rank was also calculated to determine the correlation between the cytokine levels in the aqueous humor and clinical findings. The significance of the difference in the concentration of the cytokines between eyes with a macula-off RRD and macula-on RRD was assessed by the Mann-Whitney *U* test. A *P* value of less than .05 was considered to be statistically significant.

RESULTS

NINETEEN EYES OF 19 PATIENTS (15 MEN AND 4 WOMEN) WITH RRD were included in this study. The ages of the patients ranged from 40 to 71 years with a mean of 56.9 ± 8.0 years. Preoperative BCVA was 0.50 ± 0.75 logMAR units and ranged from −0.08 to 2.00 logMAR units. One-month-postoperative BCVA was 0.27 ± 0.40 logMAR units and ranged from −0.08 to 1.22 logMAR units. Six-month-postoperative BCVA was 0.11 ± 0.23 logMAR units and ranged from −0.08 to 0.70 logMAR units. One-month-postoperative BCVA and 6-month-postoperative BCVA were better than preoperative BCVA ($P = .06$ and $P = .04$, respectively). One-month-postoperative FT was 232.7 ± 42.4 μm and ranged from 156 to 306 μm. Six-month-postoperative FT was 246.1 ± 37.1 μm and ranged from 170 to 300 μm. The mean follow-up period was 7.3 ± 3.5 months with a range of 2 to 13 months. There were 11 eyes with macula-off RRD and 8 eyes with macula-on RRD. The extent of the RRD was 1.8 ± 0.5 and ranged from 1 to 3. The mean number of retinal tears was 2.1 ± 1.8. Complete reattachment was finally obtained in all 19 eyes with RRD after surgical intervention following IVTA. No severe adverse events such as endophthalmitis or any systemic side effects were observed in the study. Seventeen patients, including 9 with an ERM and 8 with an MH, were studied as controls.

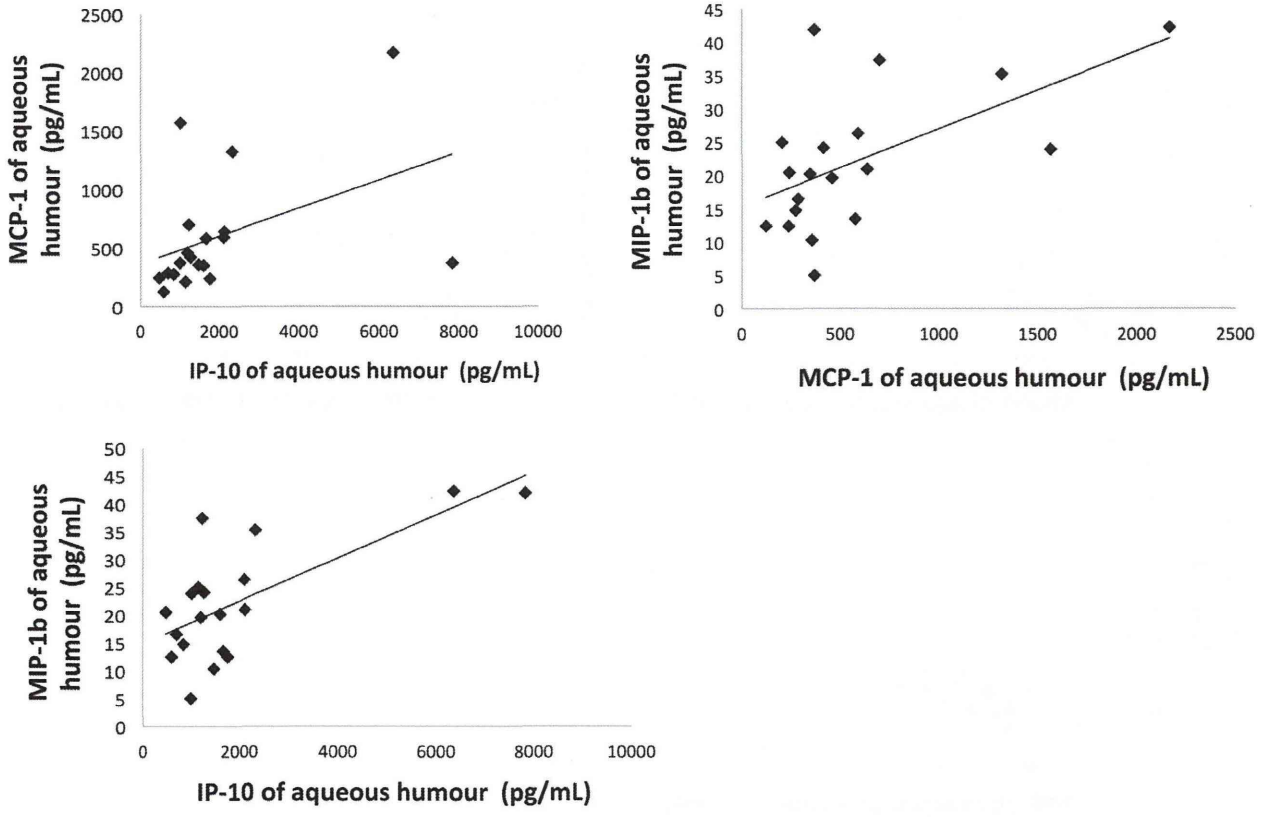

FIGURE 3. Relationship between chemokine levels in the aqueous humor after intravitreal injection of triamcinolone acetonide. (Top left) After intravitreal injection of triamcinolone acetonide, the aqueous humor level of monocyte chemotactic protein 1 (MCP-1) was significantly correlated with that of interferon γ–induced protein 10 (IP-10) ($r = 0.55$, $P = .01$). (Top right) In addition, the aqueous humor level of MCP-1 was significantly correlated with that of macrophage inflammatory protein 1β (MIP-1β) ($r = 0.56$, $P = .01$). (Bottom) The aqueous humor level of IP-10 was also significantly correlated with that of MIP-1β ($r = 0.49$, $P = .03$).

At baseline, IL-6, IFN-γ, MCP-1, MIP-1β, eotaxin, IP-10, IL-8, VEGF, and G-CSF were detected in the aqueous and were significantly higher in eyes with an RRD than in controls ($P < .001$, $P = .003$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, $P = .003$, $P < .001$, respectively) (Table). Before IVTA, the aqueous humor level of MCP-1 was significantly correlated with that of IP-10 ($r = 0.48$, $P = .04$) (Figure 1, Top left). In addition, the aqueous humor level of MCP-1 was also significantly correlated with that of MIP-1β ($r = 0.50$, $P = .03$) (Figure 1, Top right). The aqueous humor level of IP-10 was likely correlated with that of MIP-1β, but not significantly ($r = 0.44$, $P = .06$) (Figure 1, Bottom). After IVTA, the levels of MCP-1, MIP-1β, and IP-10 were significantly reduced ($P < .001$, $P = .004$, and $P = .04$, respectively) (Table). Each mediator showed a correlated decrease with the others, (MCP-1 and IP-10: $r = 0.69$, $P = .001$; MCP-1 and MIP-1β: $r = 0.57$, $P = .01$; IP-10 and MIP-1β: $r = 0.47$, $P = .04$) (Figure 2; Top left, Top right, and Bottom, respectively). After IVTA, the aqueous humor level of MCP-1 was significantly correlated with that of IP-10 ($r = 0.55$, $P = .01$) (Figure 3, Top left). In addition, the aqueous humor level of MCP-1 was significantly correlated with that of MIP-1β ($r = 0.56$, $P = .01$) (Figure 3, Top right). The aqueous humor level of IP-10 was also significantly correlated with that of MIP-1β ($r = 0.49$, $P = .03$) (Figure 3, Bottom). After IVTA, the vitreous level of MCP-1 was significantly correlated with the aqueous humor level of MCP-1 ($r = 0.52$, $P = .03$) (Figure 4, Top left). In addition, the vitreous level of IP-10 was significantly correlated with the aqueous humor level of IP-10 ($r = 0.78$, $P < .001$) (Figure 4, Top right). The vitreous level of MIP-1β was significantly correlated with the aqueous humor level of MIP-1β ($r = 0.86$, $P < .001$) (Figure 4, Bottom). After IVTA, the vitreous level of MCP-1 was significantly correlated with that of IP-10 ($r = 0.71$, $P = .001$) (Figure 5, Top left). In addition, the vitreous level of IP-10 was significantly correlated with that of MIP-1β ($r = 0.58$, $P = .01$) (Figure 5, Top right). The vitreous level of MCP-1 was likely correlated with that of MIP-1β, but not significantly ($r = 0.41$, $P = .09$) (Figure 5, Bottom).

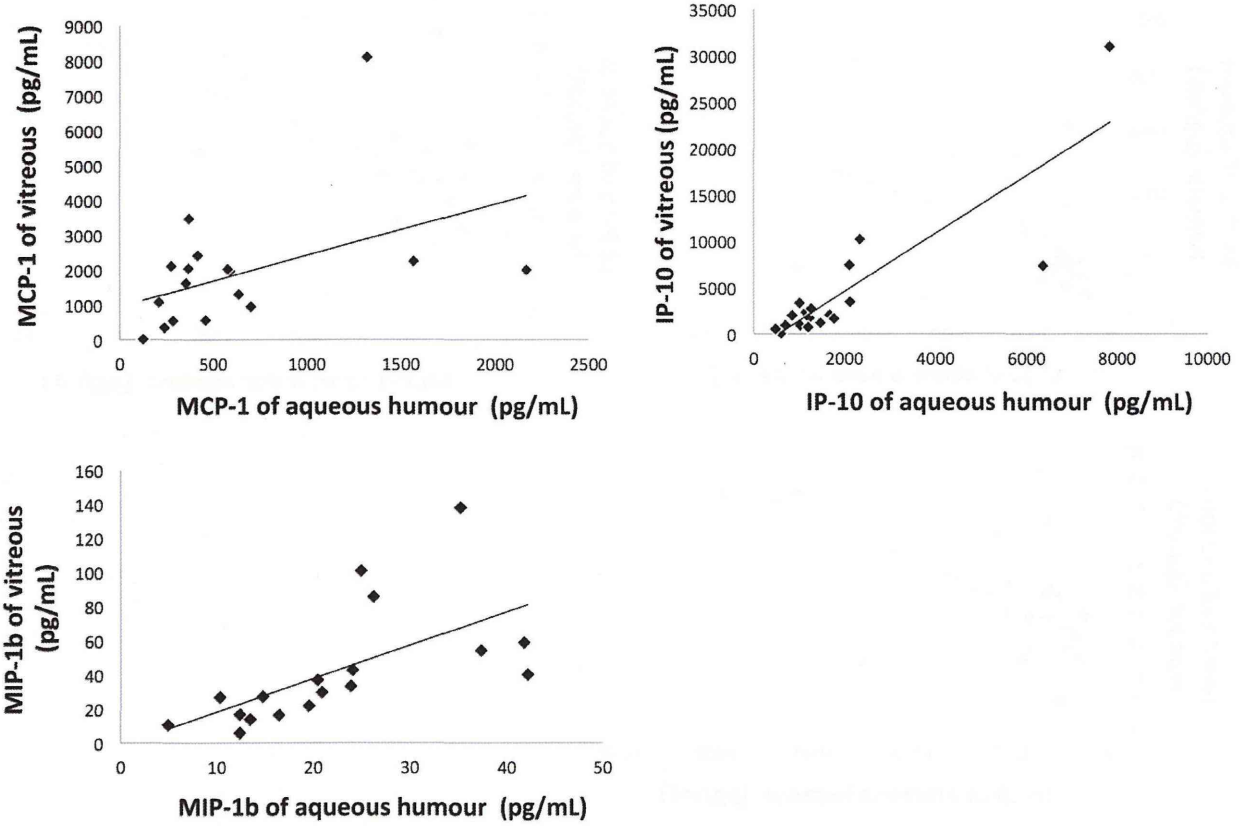

FIGURE 4. Relationship between chemokine levels in the aqueous humor and vitreous after intravitreal injection of triamcinolone acetonide. (Top left) After intravitreal injection of triamcinolone acetonide, the vitreous level of monocyte chemotactic protein 1 (MCP-1) was significantly correlated with the aqueous humor level of MCP-1 ($r = 0.52$, $P = .03$). (Top right) In addition, the vitreous level of interferon γ–induced protein 10 (IP-10) was significantly correlated with the aqueous humor level of IP-10 ($r = 0.78$, $P < .001$). (Bottom) The vitreous level of macrophage inflammatory protein 1β (MIP-1β) was significantly correlated with the aqueous humor level of MIP-1β ($r = 0.86$, $P < .001$).

Before IVTA, MCP-1 was higher in eyes with macula-off RRD (1337.2 ± 776.9 pg/mL) than in eyes with macula-on RRD (579.7 ± 256.8 pg/mL) ($P = .03$). IL-8 was also higher in eyes with macula-off RRD (27.4 ± 11.4 pg/mL) than in eyes with macula-on RRD (13.7 ± 7.4 pg/mL) ($P = .008$). Pre-IVTA eotaxin was significantly correlated with the extent of the RRD ($r = -0.60$, $P = .007$) and pre-IVTA VEGF was weakly correlated with the number of retinal tears ($r = 0.47$, $P = .04$). After IVTA, MCP-1 was higher in eyes with macula-off RRD (811.3 ± 609.2 pg/mL) than in eyes with macula-on RRD (288.5 ± 101.2 pg/mL) ($P = .006$). Post-IVTA IFN-γ and MIP-1α were significantly correlated with 1-month-postoperative BCVA ($r = 0.57$, $P = .01$ and $r = 0.66$, $P = .002$, respectively) and post-IVTA VEGF was also significantly correlated with the number of retinal tears ($r = 0.57$, $P = .01$). Post-IVTA bFGF was weakly correlated with 1-month-postoperative BCVA ($r = 0.47$, $P = .04$). Post-IVTA G-CSF was also weakly correlated with 6-month-postoperative FT ($r = -0.50$, $P = .049$).

DISCUSSION

WE SET OUT TO EVALUATE THE EFFECT OF IVTA ON mediator levels in the aqueous humor of human eyes with RRD. Our baseline measurements showed that levels of IL-6, IFN-γ, MCP-1, MIP-1β, eotaxin, IP-10, IL-8, VEGF, and G-CSF were significantly higher in eyes with RRD than in a control group. After IVTA, the levels of MCP-1, MIP-1β, and IP-10 decreased significantly; these decreases were closely correlated to each other. Thus, our study is the first to report IVTA's ability to suppress elevated levels of intraocular MCP-1, MIP-1β, and IP-10 in eyes with RRD (Figure 6). Our study additionally revealed that both before and after IVTA, MCP-1 was higher in eyes with macula-off RRD than in eyes with macula-on RRD.

Our finding that intraocular concentrations of MCP-1, IL-6, IL-8, and VEGF are significantly elevated in patients with RRD confirms existing research.[26–28] Our study also supports existing data showing that the intraocular concentration of TNF-α is not elevated in eyes with

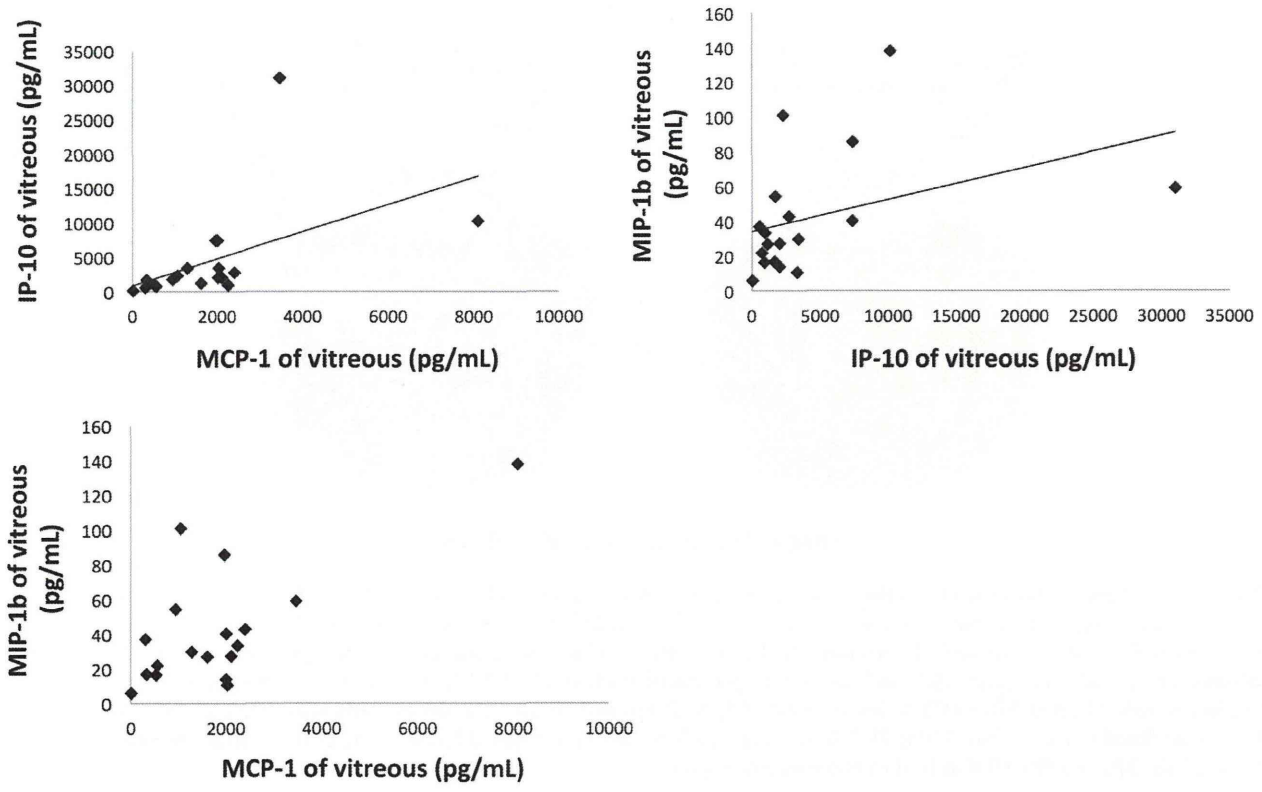

FIGURE 5. Relationship between chemokine levels in vitreous after intravitreal injection of triamcinolone acetonide. (Top left) After intravitreal injection of triamcinolone acetonide, the vitreous level of monocyte chemotactic protein 1 (MCP-1) was significantly correlated with that of interferon γ–induced protein 10 (IP-10) ($r = 0.71$, $P = .001$). (Top right) In addition, the vitreous level of IP-10 was significantly correlated with that of macrophage inflammatory protein 1β (MIP-1β) ($r = 0.58$, $P = .01$). (Bottom) The vitreous level of MCP-1 was likely correlated with that of MIP-1β, but not significantly ($r = 0.41$, $P = .09$).

RRD.[26] Interestingly, however, our data showed that corticosteroid cannot suppress TNF-α, contradicting our earlier work with an animal model.[14] The exact reason for this is unclear, but there were many differences between the earlier study and the present one besides the use of, respectively, animal and human subjects. The type of intraocular sample also differed (retinal in the animal study vs aqueous humor in the present one), as did the length of corticosteroid intervention (3 days vs 1 day), delivery method for the medication (intraperitoneal vs intravitreal injection), and method of analysis (mRNA quantification with RT-PCR vs protein quantification by multiplex bead analysis system).[14] Furthermore, it is also possible that the chemokines differ in their rate of clearance from the anterior chamber, and TNF-α might clear more slowly from the anterior chamber than MCP-1, MIP-1β, or IP-10.

The use of IVTA to treat eyes with proliferative ocular disease was part of a series of pioneering achievements in ophthalmology in the 1980s. Researchers at that time used animal models to show IVTA's capacity to inhibit fibroblast growth and significantly reduce the rate of retinal detachment.[29] Since then, it has become widely used in clinical practice in eyes with a broad range of retinal diseases, including uveitis, diabetic macular edema, retinal vein occlusion, and age-related macular degeneration.[20,21,23–25] Drug therapies in general have not yet been considered for eyes with RRD, as the priority has been improving methods for surgical reattachment. There are many patients, however, whose visual function does not recover completely, even after complete reattachment, because of retinal cell death in the time surrounding surgical intervention. Now that excellent surgical techniques, such as 25GMIVS, have established a very high reattachment rate,[1–10] the time has come to consider methods to address this gap in treatment.

We believe that IVTA, if performed promptly, can suppress photoreceptor apoptosis between RRD diagnosis and surgical intervention. The key to retinal protection during this period, as shown by initial studies using animal models, is control of the levels of several intraocular mediators, including MCP-1 and TNF-α.[14–16] These studies reported that the application of corticosteroid achieved this control for MCP-1, lowering its intraocular expression and suppressing photoreceptor death. We are the first to further demonstrate that the application of corticosteroid also reduces MCP-1 in human eyes with RRD. This is an