Clinical Trials

Efficacy and Complications of Intravitreal Rituximab Injection for Treating Primary Vitreoretinal Lymphoma

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Purpose: To assess the long-term clinical outcomes of intravitreal injections of rituximab (IVR), an anti-CD20 monoclonal antibody, to treat CD20-positive primary vitreoretinal lymphoma (PVRL).

Methods: Twenty eyes of 13 women (mean age, 66.2 ± 9.9 years) with CD20-positive PVRL were included in this prospective, interventional case series. All patients had discontinued previous intravitreal methotrexate (IVM) treatment because of severe corneal epitheliopathy. Weekly IVR injections (1 mg/0.1 ml) for 4 weeks were administered as a one-course protocol. Additional injections were administered when the PVRL recurred. The effects and the adverse events associated with IVR injections were evaluated.

Results: All patients completed a 1-year follow-up (mean observation after IVR injections, 24.7 ± 6.3 months). Before treatment, diffuse keratic precipitates (KPs), anterior vitreous cells, or both were observed in 18 (90%) eyes of 11 patients, and typical subretinal infiltrates were seen in eight (40%) eyes of six patients; all improved with one treatment course. The anterior segment lesions recurred in 11 (55%) eyes of nine patients and resolved with another course of injections. Transient IOP elevations occurred in 12 (60%) eyes of 10 patients within 3.8 ± 1.9 weeks after the first treatment course; iridocyclitis with mutton-fat KPs developed in seven (35%) eyes of six patients with elevated IOP and resolved with topical treatment. No other significant ocular complications or systemic side effects developed.

Conclusions: Injections of IVR were shown to be an efficacious alternative treatment for PVRL, although the disease recurred in approximately half of the eyes. Complications included transient IOP elevations and iridocyclitis with mutton-fat KPs that were managed topically.

Translational Relevance: The results of this trial support IVR as one element of combined modality therapy for treating PVRL patients without CNS involvement, particularly for those who respond poorly and have side effects with IVM. (<http://www.umin.ac.jp/ctr/> number, UMIN000005604)

Introduction

Primary vitreoretinal lymphoma (PVRL) is a subset of primary central nervous system lymphoma (PCNSL) that manifests as a masquerade syndrome with or without simultaneous central nervous system (CNS) involvement. The typical ocular manifestation of PVRL is the appearance of malignant lymphoid cells invading the vitreous, retina, or optic nerve head.¹⁻³ Sometimes spike-like precipitates caused by collection of tumor cells are observed. About 95% of cases of PCNSL^{1,4,5} and 98% of cases of PVRL

originate in the diffuse large B cells that express CD19 and CD20.^{1,2} CD20, a widely expressed human B-lymphocyte surface molecule, plays a role in differentiation of B-lymphocytes during B-cell ontogeny from early pre-B-cell development to differentiation into plasma cells.⁶ Blockage of CD20 leads to inhibition of B-cell proliferation and differentiation.⁶

The standard treatment modalities for PVRL have been intravenous injections of high-dose methotrexate or radiation therapy, or both. Currently, intravitreal injection of methotrexate (IVM) is the chemotherapy being used more often to treat PVRL without CNS

involvement;⁷⁻⁹ however, most patients discontinue treatment because methotrexate induces severe corneal epitheliopathy.

Rituximab (Rituxan, Genentech, Inc, San Francisco, CA), a humanized monoclonal mouse anti-CD20 antibody that binds CD20, is approved for use as the initial treatment of B-cell non-Hodgkin's lymphoma, including diffuse large B-cell lymphoma that is refractory to other chemotherapy regimens.¹⁰ The mechanism of action of this drug is thought to be induced apoptosis or complement/antibody-specific cytotoxic cell death,¹¹ but the specific mechanism is unknown. Rituximab is also useful for treating other autoimmune diseases such as rheumatoid arthritis, scleritis, ocular cicatricial pemphigoid, and thyroid-associated ophthalmopathy.¹²⁻¹⁶ However, most previous studies reported only the results of systemically administered rituximab or subconjunctival use of rituximab.¹⁷

The rationale is to administer rituximab to treat PVRL without associated CNS involvement because most cases of PVRL and PCNSL originate in the B cells and express CD20 antigen on the cell surface.¹⁸⁻²⁰ Recently, intravitreal rituximab has been used successfully to treat PVRL for short observation periods or in small case series in eyes with biopsy-proven CD20-positive PVRL with side effects of the IVM injections.^{21,22}

The current trial described the experience treating patients with PVRL who discontinued IVM injections because of severe corneal epitheliopathy and who required frequent IVM injections to control ocular symptoms. The clinical outcomes of intravitreal rituximab (IVR) injections for PVRL for more than 1 year were evaluated.

Methods

Patients

This prospective study was designed to examine the efficacy and complications of IVR injections for treating PVRL over a 1-year follow-up period. A predefined data set was obtained from the medical records of 20 eyes of 13 patients with biopsy-proven CD20-positive PVRL who were examined at the uveitis clinic at Osaka University Hospital from 2001 through 2010 and treated with injections of IVR. All patients discontinued the IVM injections because of severe corneal epitheliopathy or unresponsiveness to repeat IVM injections. The exclusion criteria were a history of glaucoma or ocular hypertension and follow up for less than 12 months after the initial

IVR injections. The institutional review board of the Osaka University Medical School approved the research protocol, and the procedures conformed to the tenets of the Declaration of Helsinki. Each patient provided informed consent after they received a detailed explanation of the procedures to be performed and the possible complications.

Examinations

Magnetic resonance imaging (MRI) and diagnostic vitrectomy were performed in patients with suspected PVRL. The vitreous specimens were submitted for cytologic and cytokine analysis. Before and after IVR treatment, ophthalmologic examinations were performed at every visit that included measurement of the best-corrected visual acuity (VA), which was converted to the logarithm of the minimum angle of resolution VA, and intraocular pressure (IOP); slit-lamp examination; and fundus examination. The vitreous concentrations of interleukin (IL)-10 and IL-6 were measured before and after the IVR injections to determine the tumoral activity.²³ MRI was performed every 3 months to assess the patient for cerebral involvement after the definitive diagnosis.

IVR Treatment Protocol

The IVR treatment protocol was a 4-week course of once weekly intravitreal injections of rituximab. The hospital pharmacy prepared the rituximab aliquots. The IVR injections (1 mg/0.1 mL) were administered using a 30-gauge needle after application of a topical anesthesia and 5% povidone iodine disinfection in the superior temporal quadrant 3.5 to 4.0 mm posterior to the limbus. Pressure was applied to the injection site with a sterile cotton swab for 1 minute to prevent leakage. After the IVR injections, the patients were instructed to apply antibiotic eye drops four times daily for 1 week. Follow-up examinations were performed weekly for 1 month and monthly thereafter. IVR injections were administered again if whitish chorioretinal lesions, increased numbers of anterior segment inflammatory cells, keratic precipitates (KPs), or vitreous opacities were observed by fundus examination, and if an increased IL-10:IL-6 ratio was found. When a relapse of PVRL was confirmed, additional IVR injections were administered until the lesions resolved. Unresponsiveness to IVR was defined as lack of symptom improvement regardless of several IVR injections. Concurrent therapy with injections of IVM was administered if the patient was intolerant of or unresponsive to IVR injections.^{24,25}

Table 1. Clinical Data and Backgrounds for Each Patient

Patient	Age (years)	Sex	Eye	IL-10/IL-6 (pg/mL) at First Examination	Duration of Total Follow Up (mo)	Duration of IVM Treatment (mo)	Initial Ocular Findings Before Treatment	
							Spike KPs	Retinal Lesions
1	52	F	R	R: 379/12.6	109	59	R+	
2	54	F	B	R: 18/6.9, L: 880/30.8	70	49	R+L+	L+
3	72	F	B	R: 9410/43.8, L: 1180/59.0	34	13	R+L+	
4	71	F	R	R: 542/16,	39	7	R+	
5	75	F	L	L: 1690/38.1	38	6	L+	
6	76	F	B	R: 21,200/808, L: 12,100/160	31	3	R+L+	R+L+
7	69	F	B	R: 96.4/8, L: 38.8/23	29	2	R+L+	R+L+
8	62	F	B	R: 6050/24.4, L: 78/4.4	36	13		R+
9	73	F	B	R: 538/44.6, L: ND	32	7	R+L+	R+
10	59	F	L	L: 588/111	40	24	L+	
11	53	F	B	R: 2730/80.4, L: 447/38.4	96	72	R+L+	
12	79	F	R	R: 775/42.8	23	3		R+
13	54	F	B	R: 879/326, L: ND	29	2	R+L+	

F, female; R, right; L, left; B, bilateral; IL, interleukin; IVM, intravitreal methotrexate; mo, months.

Results

Patient Demographic Data

The clinical data and background for each patient are summarized in Table 1. Twenty eyes of 13 patients (all women; mean patient age, 66.2 ± 9.9 years; range, 52 to 79 years) completed the 1-year follow-up after the start of IVR treatment. The mean follow-time was 46.6 ± 27.3 months (range, 23 to 109 months). During the initial presentation, 18 (90%) eyes of 11 patients had spike-like KPs, eight (40%) eyes of six patients had subretinal lesions, and one (5%) patient had CNS involvement. Before the first IVR injection, the patients had been treated with IVM injections for a median of 20.0 ± 24.1 months (range, 2 to 72 months). At the initial ocular examination before IVR treatment, seven patients primarily had sheets or clumps of vitreous cell and strong opacities, two patients primarily had white or yellowish retinal and subretinal lesions, and four patients had both.

IVR Effectiveness

The patient clinical status before and after IVR injections is summarized in Table 2. The mean total number of IVM injections was 9.2 ± 5.3 (range, 2 to 23 injections). The mean observation period after the IVR

injections was 24.7 ± 6.3 months (range, 12 to 31 months). All patients received one course of the IVR treatment protocol that resulted in initial control of the retinal invasion and a decreased number of KPs. As shown in Figure 1, the spike-like KPs dramatically improved with one course of IVR injections. The IVR injections were effective in treating the anterior segment and the vitreoretinal lesions of PVRL. Figure 2 also shows that IVM injections did not improve the retinal lesions, but they resolved with IVR. Patient 9 initially was treated several times with IVM injections without achieving complete remission. However, one course of the IVR protocol resulted in complete resolution of the retinal lesions of PVRL. Yellowish subretinal or subretinal pigment epithelial infiltrates resolved completely with one course of the IVR treatment. All patients achieved substantial clinical benefit from one course of IVR.

Ocular Recurrence after IVR

PVRL recurrences, characterized by increased anterior segment inflammatory cells, KPs, or vitreous opacities, developed within 3 months after IVR in 11 eyes (55%) of nine patients (Fig. 3, Table 2). No recurrent retinal lesions were observed. The mean time from the first IVR injection until recurrence was 3.8 ± 0.8 months (range, 3 to 5

Table 2. Clinical Status Before and After Intravitreal Injection of Rituximab

Patient	Previous Treatment (Number of IVM)	Duration of Follow Up Before IVR (mo)	Duration of Follow Up After IVR (mo)	Total Number of IVR Treatments	Periods After IVR Until Recurrence (mo)
1	R23	78	31	R8	3
2	R12, L17	50	31	R8, L4	4
3	R6, L9	14	30	R6, L8	4
4	R4, L6	8	31	R8	3
5	L9	7	31	L7	4
6	R10, L9	3	28	R10, L4	5
7	R7, L9	2	27	R6, L9	3
8	R15, L2	14	22	R4	-
9	R4, L4	10	22	R4, L4	-
10	L15	8	20	L7	5
11	R6, L18	84	17	R4, L4	-
12	R8, L3	3	20	R12	3
13	R10, L8	4	12	R4, L4	-

R, right; L, left; IVM, intravitreal methotrexate; IVR, intravitreal rituximab; mo, months; ND, not done.

months). These patients were treated with IVR and IVM injections concurrently during the follow-up period. Most patients began treatment again with IVR injections, but some patients with IOP elevations were treated with IVM injections, and one patient was treated with both. The recurrences resolved with another course of injections. The mean total number of IVR injections after the recurrence was 4.1 ± 1.7 (range, 2 to 8 injections). Among 20 eyes of 13 patients, seven (35%) eyes of four patients were followed closely without treatment because there were no recurrences. Repeat injections of IVR

and IVM resulted in dramatic improvement of the ocular symptoms (Fig. 4). During the total follow-up period, the mean total number of IVR injections was 6.3 ± 2.4 (range, 4 to 12 injections).

Adverse Events

The ocular and systemic complications associated with the IVR injections were monitored throughout the study (Table 3). No other serious ocular complications, such as endophthalmitis or retinal detachment, or systemic complications occurred

Figure 1. Patient 4. Slit-lamp examination of KPs before (A) and after (B) IVR injections. The KPs have dramatically resolved after one course of the treatment protocol.

Table 2. Extended.

Patient	IL-10/IL-6 (pg/mL) at the Time of Recurrence	IL-10/IL-6 (pg/mL) at Final Examination
1	R: 43/31.7	R: 3.0/2.9
2	R: 24/8.4	ND
3	R: 2660/1750, L: 317/48.7	ND
4	ND	ND
5	ND	L: 14/120
6	ND	ND
7	R:60/39, L: ND	ND
8	-	ND
9	-	R: 30/37.5, L: ND
10	ND	L: 2.0/15.8
11	-	ND
12	ND	R: 4.0/27
13	-	R: ND, L: 10/88.5

during the study. In the current study, the IOP exceeded 22 mmHg within 3.8 ± 1.9 weeks (range, 1 to 8 weeks) after one course of IVR injections in 12 (60%) eyes of 10 patients. Antiglaucoma drugs were administered to control the IOP. One (5%) eye required glaucoma surgery. Mutton-fat KPs and anterior segment inflammatory cells developed in seven eyes (35%) of six patients at the same time as the IOP elevations (Fig. 5); however, the symptoms responded to topical steroids.

Cerebral Involvement

Over the full follow-up period, all ocular lesions in all patients improved; however, CNS involvement ultimately developed in nine (69%) patients with no CNS lymphoma at the first visit, and the patients discontinued the ocular treatments. The patients were treated with systemic chemotherapies, intrathecal

Figure 2. Patient 9. Fundus appearance of retinal invasion of PVRL before (A) and after (B) IVM and IVR injections (C). Four injections of IVM have not successfully resolved the retinal lesions, but the lesions resolved substantially with one course of IVR injections.

Figure 3. Recurrences of PVRL within 3 months after IVR injections in 11 eyes of nine patients (55%). In patient 6, anterior segment inflammatory cells or KPs (A, D) subsided with one course of IVR injections (B, E) but recurred within 3 months (C, F).

methotrexate, and whole brain radiation concurrently (Table 3).

Discussion

IVR treatment was used successfully in patients with PVRL who could not continue with methotrexate treatment because of development of severe corneal epitheliopathy. Four weekly IVR injections controlled the PVRL lesions, which resulted in reduced retinal invasion and a decreased number of KPs. IVR injections were effective even in eyes refractory to previous treatment with methotrexate. The total numbers of injections differed among the patients because of disease severity; however, IVR injections did manage the anterior segment and retinal lesions of PVRL.

One course of IVR treatment controlled the PVRL lesions. However, in some patients, the injections were repeated to achieve complete remission. One course of IVR initially controlled the disease; however, recurrence occurred in some patients during the long time follow-up. Another course of injection and concurrent therapy with IVM was tried. Treatment selection depended on patient conditions; if IVR injections caused IOP elevation or ocular inflammation, IVM was administered. If the frequent IVM injections

caused severe corneal epitheliopathy, IVR was administered. If concurrent therapy with IVM was tolerable, the combined treatment was continued. These treatments controlled the recurrence lesion more than 6 months without any drugs.

Previously, the appropriate treatment duration had been unclear. In some patients, one course of treatment controlled tumoral growth and the drugs were stopped, but in 11 eyes of nine patients, recurrences developed within 3 months. Regarding the effective intraocular concentration of rituximab, Kim et al.²⁶ reported that intraocular injections of 1 mg of rituximab had a half-life of 4.7 days in an animal model. Rubenstein et al.²⁷ also reported that 1 µg/mL was the effective intraocular concentration of rituximab that controlled tumoral progression. Repeated IVR injections at 1-week intervals suppressed tumoral growth.²² Considering those reports, the weekly 1-mg injection protocol was sufficient to control tumoral growth at the time of injection, but the disease recurred when an effective intravitreal concentration was not achieved.

Elevated IOP was the major ocular complication of IVR injections with severe anterior segment inflammation with mutton-fat KPs, although no systemic complications were observed. Consecutive weekly injections should have been considered, but

Figure 4. Representative case (patient 7) of repeated IVR injections. Both eyes had recurrent lesions and underwent multiple IVR injections in combination with IVM injections with subsequent improvement of the subretinal lesions. The patient received a total of 18 injections (nine IVM and nine IVR) in the left eye. (A) Multiple retinal lesions are seen at the first examination. (B) One month after multiple IVR injections in combination with IVM injections, the lesions improved. (C) The retinal lesions ultimately resolved during 1 year of follow-up.

due to the IOP elevations, the IVR injections were discontinued in seven eyes of six patients. Before considering the ocular side effects, the mechanism of action of rituximab must be considered. The activity of rituximab may depend on its interaction with subsets of leukocytes, such as macrophages, especially through antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cell lysis of tumoral cells, and induction of apoptosis.^{28–30} Release of tumor necrosis factor alpha is reported to be a major biologic event associated with rituximab treatment.³¹ Taken together, it was speculated that rituximab in the anterior chamber bound the malignant cells and activated some types of leukocytes, such as macrophages, and through ADCC mutton-fat KPs devel-

oped as seen in active anterior segment uveitis. In fact, histologic analysis of the anterior chamber inflammatory cells showed macrophage and lymphocyte infiltrations (data not shown). Mutton-fat KPs were associated in one set of clinical signs corresponding to a granulomatous reaction in the anterior segment. The elevated IOP and severe anterior segment inflammation with mutton-fat KPs were controlled with topical steroids and antiglaucoma eye drops, but one (5%) patient required glaucoma surgery, which suggested that the IOP elevations and appearance of mutton-fat KPs should be monitored carefully after IVR was injected.

The results in the current case series indicated that one course of IVR treatment was as efficacious

Table 3. Ocular Complications of Intravitreal Rituximab

Patient	IOP Elevation		Mutton Fat KPs	CNS Involvement	Concurrent Therapies After IVR
	Elevation	Weeks after IVR			
1	+	3	R+	Y	S-chemo, IT-MTX, WBR
2	+	4	-	Y	IT-MTX, WBR
3	+	1	R+	Y	S-chemo, WBR
4	+	1	R+	Y	S-chemo
5	+	4	L+	Y	S-chemo, WBR
6	+	5	-	Y	IT-MTX, WBR, S-chemo
7	+	1	-	Y	S-chemo, IT-MTX, WBR
8	-	-	-	N	S-chemo, IT-MTX
9	+	4	R+, L+	N	-
10	-	-	-	N	S-chemo, IT-MTX
11	+	8	L+	Y	IT-MTX
12	-	-	-	N	-
13	+	4	-	Y	S-chemo, IT-MTX, WBR

IVR, intravitreal rituximab; IOP, intraocular pressure; CNS, central nervous system; S-chemo, systemic chemotherapy; IT-MTX, intrathecal MTX; WBR, whole brain radiation; R, right; L, left; Y, yes; N, no.

for treating PVRL as IVM injections. However, IVR monotherapy did not induce complete remission of PVRL, because the PVRL recurred and concomitant therapies such as IVM injection and systemic injection of methotrexate were used in 11 patients. After the recurrences, the efficacy of the IVR injections decreased. The mechanism of action of rituximab remained unclear, but a potential resistance mechanism has been proposed. For instance, decreased or absent CD20 expression on lymphoma cells or deficient post-CD20 binding B-cell signaling is supposed to be involved in clinical resistance.³² One criterion for stopping the IVR injections was the development of elevated IOP with severe inflammation. However, criteria for stopping IVR treatment for patients who responded well to the medication was not established. In addition, there was no established index for determining the appropriate dose of IVR for complete tumoral eradication. To manage the side effects of severe corneal epitheliopathy with IVM treatments and decrease the frequency of intraocular injections, it will be important to find treatment modalities of IVR injections with or without combining them with IVM injections.

The clinical ocular symptoms of PVRL decreased significantly with IVR treatment; however, nine (69%) patients ultimately developed CNS lesions during follow up. It has been reported that 50% to 90% of patients with vitreoretinal lymphoma ultimately developed CNS involvement, and vitreoretinal lympho-

ma has been reported in up to 15% of patients with PCNSL.^{33–36} Intravenous injection of rituximab prolonged survival in patients with systemic large B-cell lymphoma but did not affect the prognosis of CNS lymphoma, because the drugs do not penetrate the blood brain barrier. Our data showed that IVR injections controlled the retinal lesions of lymphoma, but focal administration alone did not suppress progression of the CNS tumor. It is controversial if isolated PVRL should be treated locally alone or systemically in combination with a protocol that presumes CNS involvement. Because all patients in the current study underwent additional local treatment such as IVM injections or additional systemic infusion of methotrexate or radiation therapy, a definitive conclusion could not be drawn about the clinical effectiveness of IVR injections for preventing CNS progression. Thus, the limited effectiveness of IVR injections when used alone must be considered, and cerebral lesions must be monitored because cerebral involvement might occur during long-term follow-up.

In summary, transient IOP elevations and iridocyclitis with mutton-fat KPs were major complications that were manageable with topical treatments. Intensive studies should be undertaken to address treatment of the primary lesions of PVRL. However, the current results indicated that IVR injections were efficacious for treating the anterior segment retinal lesions and recurrent lesions of PVRL.

Figure 5. Three representative cases of severe iridocyclitis with mutton-fat KPs with elevated IOP: patient 9 (A), patient 5 (B), and patient 11 (C). The symptoms resolved with topical steroid treatment.

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References

1. Commins DL. Pathology of primary central nervous system lymphoma. *Neurosurg Focus*. 2006;21:E2.
2. Schabet M. Epidemiology of primary CNS lymphoma. *J Neurooncol*. 1999;43:199–201.
3. Hochberg FH, Baehring JM, Hochberg EP. Primary CNS lymphoma. *Nat Clin Pract Neurol*. 2007;3:24–35.
4. Bataille B, Delwail V, Menet E, et al. Primary intracerebral malignant lymphoma: report of 248 cases. *J Neurosurg*. 2000;92:261–266.
5. Kadoch C, Treseler P, Rubenstein JL. Molecular pathogenesis of primary central nervous system lymphoma. *Neurosurg Focus*. 2006;21:E1.

6. Tedder TF, Klejman G, Schlossman SF, Saito H. Structure of the gene encoding the human B lymphocyte differentiation antigen CD20 (B1). *J Immunol.* 1989;142:2560–2568.
7. Fishburne BC, Wilson DJ, Rosenbaum JT, Neuwelt EA. Intravitreal methotrexate as an adjunctive treatment of ocular lymphoma. *Arch Ophthalmol.* 1997;115:1152–1156.
8. Smith JR, Rosenbaum JT, Wilson DJ, et al. Role of intravitreal methotrexate in the management of primary central nervous system lymphoma with ocular involvement. *Ophthalmology.* 2002;109:1709–1716.
9. de Smet MD, Vancs VS, Kohler D, Solomon D, Chan CC. Intravitreal chemotherapy for the treatment of recurrent intraocular lymphoma. *Br J Ophthalmol.* 1999;83:448–451.
10. Scott SD. Rituximab: a new therapeutic monoclonal antibody for non-Hodgkin's lymphoma. *Cancer Pract.* 1998;6:195–197.
11. Nielsen CH, El Fassi D, Hasselbalch HC, Bendtzen K, Hegedüs LC. *Expert Opin Biol Ther.* 2007;7:1061–1078.
12. van Vollenhoven RF, Emery P, Bingham CO III, et al. Long term safety of patients receiving rituximab in rheumatoid arthritis clinical trials. *J Rheumatol.* 2010;37:558–567.
13. Cheung CM, Murray PI, Savage CO. Successful treatment of Wegener's granulomatosis associated scleritis with rituximab. *Br J Ophthalmol.* 2005;89:1542.
14. Khanna D, Chong KK, Afifiyan NF, et al. Rituximab treatment of patients with severe, corticosteroid-resistant thyroid-associated ophthalmopathy. *Ophthalmology.* 2010;117:133–139.e2.
15. Foster CS, Chang PY, Ahmed AR. Combination of rituximab and intravenous immunoglobulin for recalcitrant ocular cicatricial pemphigoid: a preliminary report. *Ophthalmology.* 2010;117:861–869.
16. Shetty RK, Adams BH, Tun HW, Runyan BR, Menke DM, Broderick DF. Use of rituximab for periocular and intraocular mucosa-associated lymphoid tissue lymphoma. *Ocul Immunol Inflamm.* 2010;18:110–112.
17. Ferreri AJ, Govi S, Colucci A, Crocchiolo R, Modorati G. Intralesional rituximab: a new therapeutic approach for patients with conjunctival lymphomas. *Ophthalmology.* 2011;118:24–28.
18. Rubenstein JL, Treseler P, O'Brien JM. Pathology and genetics of primary central nervous system and intraocular lymphoma. *Hematol Oncol Clin North Am.* 2005;19:705–717.
19. Choi JY, Kafkala C, Foster CS. Primary intraocular lymphoma: a review. *Semin Ophthalmol.* 2006;21:125–133.
20. Grimm SA, Pulido JS, Jahnke K, et al. Primary intraocular lymphoma: an International Primary Central Nervous System Lymphoma Collaborative Group Report. *Ann Oncol.* 2007;18:1851–1855.
21. Kitzmann AS, Pulido JS, Mohny BG, et al. Intraocular use of rituximab. *Eye (Lond).* 2007;21:1524–1527.
22. Ohguro N, Hashida N, Tano Y. Effect of intravitreal rituximab injections in patients with recurrent ocular lesions associated with central nervous system lymphoma. *Arch Ophthalmol.* 2008;126:1002–1003.
23. Chan CC, Whitcup SM, Solomon D, Nussenblatt RB. Interleukin-10 in the vitreous of patients with primary intraocular lymphoma. *Am J Ophthalmol.* 1995;120:671–673.
24. Itty S, Pulido JS. Rituximab for intraocular lymphoma. *Retina.* 2009;29:129–132.
25. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. *Oncologist.* 2011;16:1589–1599.
26. Kim H, Csaky KG, Chan CC, et al. The pharmacokinetics of rituximab following an intravitreal injection. *Exp Eye Res.* 2006;82:760–766.
27. Rubenstein JL, Combs D, Rosenberg J, et al. Rituximab therapy for CNS lymphomas: targeting the leptomeningeal compartment. *Blood.* 2003;101:466–468.
28. Golay J, Cittera E, Di Gaetano N, et al. The role of complement in the therapeutic activity of rituximab in a murine B lymphoma model homing in lymph nodes. *Haematologica.* 2006;91:176–183.
29. Selenko N, Maidic O, Draxier S, et al. CD20 antibody (C2B8)-induced apoptosis of lymphoma cells promotes phagocytosis by dendritic cells and cross-priming of CD8+ cytotoxic T cells. *Leukemia.* 2001;15:1619–1626.
30. Takami A, Hayashi T, Kita D, Nishimura R, Asakura H, Nakao S. Treatment of primary central nervous system lymphoma with induction of complement-dependent cytotoxicity by intraventricular administration of autologous-serum-supplemented rituximab. *Cancer Sci.* 2006;97:80–83.

31. Bienvenu J, Chvetzoff R, Salles G, et al.; Groupe d'Etude des Lymphomes de l'Adulte. Tumor necrosis factor alpha release is a major biological event associated with rituximab treatment. *Hematol J*. 2001;2:378–384.
32. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. *Oncogene*. 2003;22:7359–7368.
33. Peterson K, Gordon KB, Heinemann MH, DeAngelis LM. The clinical spectrum of ocular lymphoma. *Cancer*. 1993;72:843–849.
34. Cassoux N, Merle-Beral H, Leblond V, et al. Ocular and central nervous system lymphoma: clinical features and diagnosis. *Ocul Immunol Inflamm*. 2000;8:243–250.
35. Hochberg FH, Miller DC. Primary central nervous system lymphoma. *J Neurosurg*. 1988;68:835–853.
36. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. *Oncologist*. 2011;16:1589–1599.