ORIGINAL ARTICLE

Intravitreal bevacizumab versus triamcinolone acetonide for uveitic cystoid macular edema: a meta-analysis

Zi Ye Jin,[1] MD, Xiu Ying Wang, MD, Yong Tao,[3] MD, Dan Zhu,[1] MD, Jost B. Jonas[4] MD
[1]The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia, China
[2]Department of Ophthalmology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China
[3]Department of Ophthalmology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China.
[4]Department of Ophthalmology, Medical Faculty Mannheim of the Ruprecht-Karls University, Heidelberg, Germany

Zi Ye Jin and Xiu Ying Wang contributed equally and share the first authorship

Correspondence and reprint requests:
Prof. Dan Zhu, The Affiliated Hospital of Inner Mongolia Medical University, No.1 Tongdaobei Street, 010050, Hohhot, Inner Mongolia, China.
Email: zhudan1968@163.com

Abstract

Purpose: To carry out a meta-analysis of studies comparing intravitreal bevacizumab (IVB) with intravitreal triamcinolone acetonide (IVT) in the treatment of uveitic cystoid macular edema.
Methods: Relevant publications were identified through PubMed, EMBASE, and the Cochrance Controlled Trials Register. Patients prescribed IVB verus IVT were compared in terms of central macular thickness (CMT) and best-corrected visual acuity (BCVA) at baseline and 1, 3, and 6 months after treatment.
Results: Four comparative studies with 72 eyes in the IVB group and 76 eyes in the IVT group were included. Funnel plots, the Egger method, and Begg method did not show any publication bias. The IVT and IVB groups were comparable in BCVA at 1 month (weighted mean deviation [WMD] = 0.06, 95% confidence interval [CI] = -0.05-0.16, p = 0.31), 3 months (WMD = 0.09, 95% CI= -0.01-0.18, p = 0.08), and 6 months (WMD = 0.04, 95% CI = -0.02-0.11, p = 0.20), as well as change in CMT at one month (WMD = 5.17, 95% CI = -9.2-19.5, p = 0.48) and 3 months (WMD = 43.3, 95% CI = -11.6-98.2, p = 0.12). At 6 months, change in CMT was higher in the IVT than IVB group (WMD = 40.6, 95% CI = 8.2-73.0, p = 0.01).
Conclusion: At 6 months after injection, IVT was more effective than IVB in reducing CMT.

Key words: Bevacizumab; Macular edema; Meta-analysis; Triamcinolone acetonide; Uveitis

Introduction

Uveitis is an etiologically heterogeneous disease characterized by inflammation of the iris, ciliary body or choroid. It can lead to a loss in visual acuity, usually due to cystoid macular edema.[1-4] Cystoid macular edema is usually treated with topical application of non-steroidal anti-inflammatory drugs or steroidal drugs and, if not sufficient, systemic application of anti-inflammatory medication.[5] Intravitreal triamcinolone acetonide (IVT) and intravitreal bevacizumab (IVB) have been applied in patients with uveitic cystoid macular edema resistant to topical medication.[6-13] Indication for use of anti-vascular endothelial

growth factor (VEGF) drugs for uveitis macular edema was elevated intraocular concentration of VEGF.[14] Triamcinolone counteracts VEGF in a non-specific way, whereas anti-VEGF drugs as antibodies with a high specificity neutralize the effect of VEGF.

Triamcinolone and bevacizumab differ in their pharmacokinetic properties and side effects. This study aimed to carry out a meta-analysis of studies that compared IVT with IBV in terms of their efficacy and side effects in the treatment of uveitic cystoid macular edema.

Methods

This study was approved by the ethics committee of the Beijing Chaoyang Hospital, Capital Medical University. Patient consent was not required. Electronic databases of PubMed, EMBASE, and Cochrane Controlled Trials Register were searched for studies up to November 30, 2016, using key words 'bevacizumab', 'triamcinolone acetonide', 'avastin', and 'uveitic cystoid macular edema'. References were also searched for relevant articles. There was no language restriction.

Inclusion criteria were (1) randomized controlled trials and high-quality comparative studies comparing IVB with IVT for cystoid macular edema; and (2) availability of data on age, gender, refractive error, history of disease, best-corrected visual acuity (BCVA), and central macular thickness (CMT); and (3) number of patients >20. Exclusion criteria were (1) IVB or IVT was not the only treatment or the efficacy of the treatment was not determined; (2) study design involved inappropriate randomization or insufficient information about the study population or clear definition of the disease; and (3) repeated publication; for articles published by the same groups of authors, only the earliest or those with the largest data volume were used.

Data extracted included (1) title, author, publication data, study site; (2) number of patients, age, dosage of the drugs applied, number of intravitreal injections, and follow-up duration; and (3) BCVA and CMT.

The meta-analysis was carried out using the Cochrane Review Manager (RevMan; version 5.0 software). The treatment effect was estimated by means of weighted mean deviation (WMD) of BCVA and CMT. 95% confidence intervals (CI) were presented. Random effects models were used, taking into account the possibility of heterogeneity between studies (tested by the Z test). A p value <0.05 was considered statistically significant. Publication bias was assessed using a funnel plot, Egger´s linear regression method, and the Begg rank correlation test.

Results

A total of 43 articles were identified; 39 were excluded and the remaining four were reviewed.[15-18] The allocation to the IVB or IVT group was randomized; the sample size ranged from 21 to 60 eyes; and follow-up ranged from 6 to 9 months (**Table 1**). There were 72 eyes in the IVB group and 76 eyes in IVT group. The two groups did not differ significantly in age, gender, refractive error, baseline BCVA and CMT, or disease duration. No patients had a systemic disorder that may have caused the uveitis or an ocular disease other than that causing uveitis. Patients with a history of other diseases causing macular edema (such as diabetes mellitus and retinal vein occlusions) were excluded. All patients had undergone a detailed ophthalmological examination, including assessment of BCVA, a fundus examination with the pupils medically dilated, color fundus photography, fluorescein angiography, indocyanine green angiography, and optical coherence tomography of the retina.

All four studies reported BCVA at 1, 3, and 6 months after initial treatment; the values were converted to the logarithm of the minimum angle of resolution (logMAR) and were summarized by means of meta-analysis of I^2 = 50%, 78%, and 79%, respectively. The two groups did not differ significantly in BCVA at 1 month (WMD = 0.06, 95% CI = -0.05-0.16, p = 0.31), 3 months (WMD = 0.09, 95% CI = -0.01-0.18, p = 0.08), or 6 months (WMD = 0.04, 95% CI = -0.02-0.11, p = 0.20) [**Table 2**].

All four studies reported CMT at 1, 3, and 6 months after

Table 1. Characteristics of studies comparing intravitreal bevacizumab (IVB) with intravitreal triamcinolone acetonide (IVT) in the treatment of uveitic cystoid macular edema

Study	Study design	Population	No. of patients with IVB vs IVT	Mean±SD patient age (years)	IVB vs IVT dose (mg)	Follow-up (months)	Etiology	Degree of control of intraocular inflammation
Bae et al,[18] 2011	Retrospective non-randomized controlled	Korea	10 vs 11	54.8±16.6	1.25 vs 4.0	6	None had a systemic or ocular disease other than the one causing uveitis or non-infectious uveitis	Complete control of uveitis (no cells in the anterior chamber)
Lasave et al,[15] 2009	Retrospective non-randomized controlled	Multinational	16 vs 20	45.6±13.2	2.5 vs 4.0	6		
Rahimi et al,[17] 2012	Randomized	Iran	31 vs 29	23.2±11.7	1.25 vs 4.0	6		
Soheilian et al,[16] 2010	Randomized	Iran	15 vs 16	33.1±16.2	1.25 vs 2.0	9		

Table 2. Best corrected visual acuity (BCVA) at 1, 3, and 6 months after intravitreal bevacizumab (IVB) or intravitreal triamcinolone acetonide (IVT)

Study	IVB		IVT		Weight (%)	Mean difference
	Mean±SD BCVA	No. of patient	Mean±SD BCVA	No. of patients		IV, Random, 95% CI
At 1 month*						
Bae et al,[18] 2011	0.47±0.47	10	0.38±0.21	11	9.4	0.09 (-0.23, 0.41)
Lasave et al,[15] 2009	1.1±0.4	16	0.8±0.4	20	12.7	0.30 (0.04, 0.56)
Rahimi et al,[17] 2012	0.14±0.08	31	0.15±0.08	29	49.6	-0.01 (-0.05, 0.03)
Soheilian et al,[16] 2010	0.76±0.27	15	0.71±0.04	16	28.3	0.05 (-0.09, 0.19)
Total (95% CI)		**72**		**76**	**100.0**	**0.06 (-0.05, 0.16)**
At 3 months†						
Bae et al,[18] 2011	0.06±0.06	10	0.07±0.06	11	38.6	-0.01 (-0.06, 0.04)
Lasave et al,[15] 2009	1±0.3	16	0.7±0.6	20	13.8	0.30 (0.07, 0.53)
Rahimi et al,[17] 2012	0.52±0.45	31	0.41±0.21	29	17.1	0.11 (-0.07, 0.29)
Soheilian et al,[16] 2010	0.66±0.1	15	0.56±0.02	16	35.3	0.10 (0.05, 0.15)
Total (95% CI)		**72**		**76**	**100.0**	**0.09 (-0.01, 0.18)**
At 6 months‡						
Bae et al,[18] 2011	0.54±0.39	10	0.45±0.36	11	4.2	0.09 (-0.23, 0.41)
Lasave et al,[15] 2009	0.8±0.4	16	0.7±0.3	20	7.2	0.10 (-0.14, 0.34)
Rahimi et al,[17] 2012	0.03±0.04	31	0.03±0.04	29	46.2	0.00 (-0.02, 0.02)
Soheilian et al,[16] 2010	0.6±0.07	15	0.52±0.02	16	42.4	0.08 (0.04, 0.12)
Total (95% CI)		**72**		**76**	**100.0**	**0.04 (-0.02, 0.11)**

* *Heterogeneity: $Tau^2 = 0.01$, $Chi^2 = 6.03$, $df = 3$ ($p = 0.11$), $I^2 = 50\%$; test for overall effect: $Z = 1.02$ ($p = 0.31$)*
† *Heterogeneity: $Tau^2 = 0.01$, $Chi^2 = 13.85$, $df = 3$ ($p = 0.003$), $I^2 = 78\%$; test for overall effect: $Z = 1.77$ ($p = 0.08$)*
‡ *Heterogeneity: $Tau^2 = 0.00$, $Chi^2 = 14.60$, $df = 3$ ($p = 0.002$), $I^2 = 79\%$; test for overall effect: $Z = 1.28$ ($p = 0.20$)*

initial treatment; heterogeneity between studies was low with I^2 of 0%, 82%, and 86%, respectively. The two groups did not differ significantly in change in CMT at 1 month (WMD = 5.17, 95% CI = 9.20-19.53, p = 0.48) or 3 months (WMD = 43.3, 95% CI = -11.6-98.2, p = 0.12). At 6 months, change in CMT was higher in the IVT than IVB group (WMD = 40.6, 95% CI = 8.2-73.0, p = 0.01) [**Table 3**].

Publication bias

Based on funnel plots for the analysis of BCVA and CMT, no obvious evidence of publication bias was found for the treatment outcome estimates (BCVA and CMT at 3 months) [**Figure**]. Nonetheless, the number of enrolled studies was relatively low; Egger's method and Begg's method were additionally applied to measure any publication bias and found no significant publication bias (BCVA at 3 months: Egger method, p = 0.86; Begg method, p = 0.57; CMT at 3 months: Egger method, p = 0.26; Begg method, p = 0.12).

Discussion

In our meta-analysis, IVT and IVB did not differ significantly in improvement of BCVA or CMT up to 6 months after initial treatment, except that at 6 months IVT was more effective than IVB in reducing CMT. Nonetheless, triamcinolone can lead to a profound increase in intraocular pressure (IOP), particularly in younger patients. Patients with uveitic macular edema are usually <70 years old; their risk of a triamcinolone-induced ocular hypertension and secondary steroid-induced open-angle glaucoma may therefore be higher than for those with diabetic macular edema. In addition, the underlying uveitis can independently be associated with elevated IOP. Nonetheless, if uveitis results in ocular hypotony and uveitic macular edema, IVT may be used in this special clinical situation.

In the Lasave et al study,[15] IOP was medically controlled with topical anti-glaucoma medications in all 20 but one (5%) eye, which later required trabeculectomy, whereas another eye showed a marked progression of cataract in the IVT group. In the Bae et al study,[18] IOP increased within one day to 8 weeks of IVT application in 11 patients; IOP spontaneously decreased in five patients, and was medically controlled by topical anti-glaucomatous medications or by systemic acetazolamide in four. Anti-glaucomatous filtration surgery was required in one patient. As no change was detected in the optic disk appearance in any of the patients, the intravitreal steroid-induced IOP increase could have been secondary to ocular hypertension rather than open-angle glaucoma.[18] In the remaining two studies,[16,17] patients who developed a steroid-induced IOP rise were well controlled with topical anti-glaucoma medication; systemic therapy or filtration surgery was not required, and there was no change in the optic nerve head appearance.

Besides IVT, both intravitreal slow-release devices of dexamethasone (orzudex) and fluocinolone (Retisert) demonstrate an intraocular anti-inflammatory effect in patients with uveitis and result in decreased macular edema and increased visual acuity.[19-25] Nonetheless, neither has

Table 3. Central macular thickness (CMT) at 1, 3, and 6 months after intravitreal bevacizumab (IVB) or intravitreal triamcinolone acetonide (IVT)

Study	IVB		IVT		Weight (%)	Mean difference
	Mean±SD CMT	No. of patient	Mean±SD CMT	No. of patients		IV, Random, 95% CI
At 1 month*						
Bae et al,[18] 2011	220.6±239	10	227.1±95.1	11	0.8	-6.50 (-164.93, 151.93)
Lasave et al,[15] 2009	332.1±120.7	16	303.3±164	20	2.4	28.80 (-64.28, 121.88)
Rahimi et al,[17] 2012	254.54±30.15	31	251.75±30.41	29	87.8	2.79 (-12.54, 18.12)
Soheilian et al,[16] 2010	328.3±72.9	15	305.2±62.1	16	9.0	23.10 (-24.72, 70.92)
Total (95% CI)		**72**		**76**	**100.0**	**5.17 (-9.20, 19.53)**
At 3 months†						
Bae et al,[18] 2011	260.6±229.6	10	269.5±158.1	11	8.2	-8.90 (-179.13, 161.33)
Lasave et al,[15] 2009	323.4±108.1	16	289.4±141.2	20	20.9	34.00 (-47.46, 115.46)
Rahimi et al,[17] 2012	233.9±12.56	31	218.13±29	29	37.9	15.77 (4.33, 27.21)
Soheilian et al,[16] 2010	386.2±50.4	15	292.4±52.2	16	33.0	93.80 (57.68, 129.92)
Total (95% CI)		**72**		**76**	**100.0**	**43.33 (-11.56, 98.23)**
At 6 months‡						
Lasave et al,[15] 2009	344.7±135	16	296±134.4	20	10.5	48.70 (-39.87, 137.27)
Rahimi et al,[17] 2012	221.06±12.13	31	199.27±27.64	29	46.1	21.79 (10.86, 32.72)
Soheilian et al,[16] 2010	345±13.2	15	286.4±30	16	43.4	58.60 (42.45,74.75)
Total (95% CI)		**62**		**65**	**100.0**	**40.59 (8.16, 73.03)**

* *Heterogeneity: Tau² = 0.00, Chi² = 0.90, df = 3 (p = 0.83), I² = 0%; test for overall effect: Z = 0.70 (p = 0.48)*
† *Heterogeneity: Tau² = 2034.79, Chi² = 16.50, df = 3 (p = 0.0009), I² = 82%; test for overall effect: Z = 1.55 (p = 0.12)*
‡ *Heterogeneity: Tau² = 563.00, Chi² = 13.81, df = 2 (p = 0.001), I² = 86%; test for overall effect: Z = 2.45 (p = 0.01)*

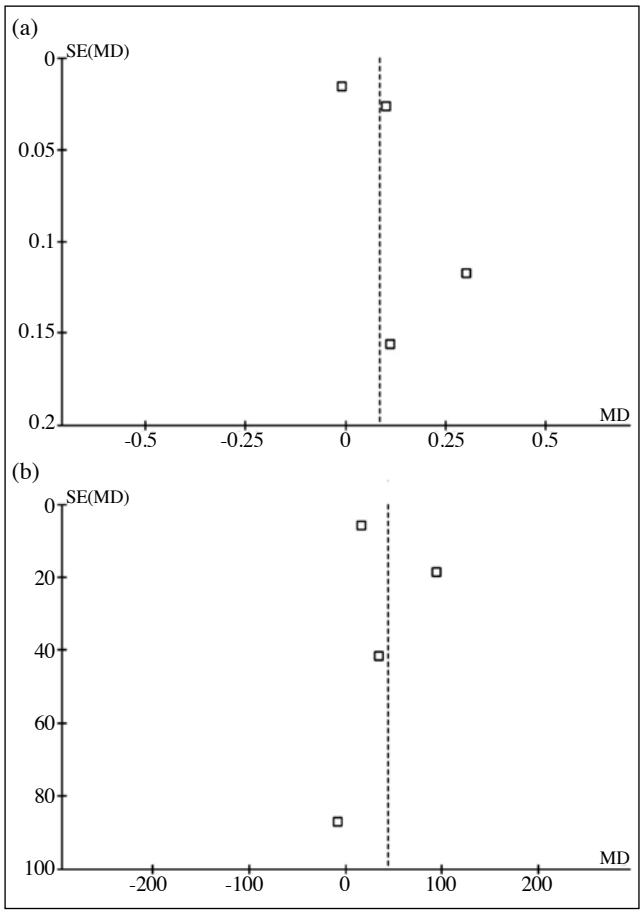

Figure. Funnel plots for publication bias: (a) best corrected visual acuity and (b) central macular thickness at 3 months after treatment.

been compared with intravitreally applied anti-VEGF drugs or IVT as treatment for uveitis.

There were limitations to our study. Only a few clinical studies were included in our meta-analysis, and each contained relatively few patients; the etiology of uveitis was heterogeneous. In addition, different studies used different optical coherence tomography devices; measurements could not be directly compared between studies. Despite this, funnel plots did not reveal any obvious evidence of a publication bias. Moreover, the follow-up duration was limited to 6 months; longer-term outcome was not known. The etiology of uveitis was usually not given or fully presented; results of our study can therefore refer only to the group of non-infectious uveitis. Information about the type of systemic treatment that might have been previously applied, and the degree of control of intraocular inflammation at the time of intraocular injection were not fully described. Periocular injection of steroids including subconjunctival application of steroids has been commonly used to treat edema in patients with uveitis who are non-responsive to topical steroids or non-steroidal anti-inflammatory drugs. Our study focused on comparison of intravitreal injection of drugs for uveitic macular edema; the method of peribulbar steroid injection was not evaluated.

Conclusion

IVT and IVB achieved comparable improvements in BCVA and reduction in CMT in patients with uveitic macular edema, although IVT was more effective than IVB in

reducing CMT at 6 months. This slight advantage of IVT may be outweighed by the disadvantage of a steroid-induced ocular hypertension with the risk of conversion to temporary secondary open-angle glaucoma. With respect to safety and visual improvement, IVB may be the first choice for treatment of uveitic macular edema.

Acknowledgement

This study was supported by National High Technology Research and Development Program of China (No. 2015AA020949), Beijing Nova Program (Z15111000030000), Program for New Century Excellent Talents in University (No: NCET-12-0010), and the Fok Ying-Tong Education Foundation (No. 141038). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration

Jost B. Jonas is a consultant for Allergan, Merck Sharp & Dohme, Alimera, Boehringer Ingelheim, and Sanofi, as well as patent holder with Biocompatible UK (treatment of eye diseases using encapsulated cells encoding and secreting neuroprotective factor and/or anti-angiogenic factor; patent number: 20120263794), and patent application with University of Heidelberg (agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia; Europäische Patentanmeldung 15 000 771.4). All other authors have disclosed no conflicts of interest.

References

1. *Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80:332-6.*
2. *Okhravi N, Lightman S. Cystoid macular edema in uveitis. Ocul Immunol Inflamm. 2003;11:29-38.*
3. *Lardenoye CW, Rothova A, Van Kooij B. Impact of macular edema on visual acuity in uveitis. Ophthalmology. 2006;113:1446-9.*
4. *Rothova A. Inflammatory cystoid macular edema. Curr Opin Ophthalmol. 2007;18:487-92.*
5. *Cordero Coma M, Sobrin L, Onal S, Christen W, Foster CS. Intravitreal bevacizumab for treatment of uveitic macular edema. Ophthalmology. 2007;114:1574-9.*
6. *Baffi J, Fine HF, Reed GF, Csaky KG, Nussenblatt RB. Aqueous humor and plasma vascular endothelial growth factor in uveitis-associated cystoid macular edema. Am J Ophthalmol. 2001;132:794-6.*
7. *Young S, Larkin G, Branley M, Lightman S. Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis. Clin. Experiment Ophthalmol. 2001;29:2-6.*
8. *Degenring RF, Jonas JB. Intravitreal injection of triamcinolone acetonide as treatment of chronic uveitis. Br J Ophthalmol. 2003;87:361.*
9. *Angunawela RI, Heatley CJ, Williamson TH, et al. Intravitreal triamcinalone acetonide for refractory uveitic cystoid macular oedema: longterm management and outcome. Acta Ophthalmol Scand. 2005;83:595-9.*
10. *Kok H, Lau C, Maycock N, McCluskey P, Lightman S. Outcome of intravitreal triamcinolone in uveitis. Ophthalmology. 2005;112:1916.e1-7.*
11. *Finger PT, Chin K. Anti-vascular endothelial growth factor bevacizumab (Avastin) for radiation retinopathy. Arch Ophthalmol. 2007;125:751-6.*
12. *Becker MD, Heinz C, Mackensen F, Heiligenhaus A. Intravitreal bevacizumab (Avastin) as a treatment for refractory macular edema in patients with uveitis: a pilot study. Retina. 2008;28:41-5.*
13. *Sallam A, Comer RM, Chang JH, et al. Short-term safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema in children. Arch Ophthalmol. 2008;126:200-5.*
14. *Weiss K, Steinbrugger I, Weger M, et al. Intravitreal VEGF levels in uveitis patients and treatment of uveitic macular oedema with intravitreal bevacizumab. Eye (Lond). 2009;23:1812-8.*
15. *Lasave AF, Zeballos DG, El-Haig WM, Díaz-Llopis M, Salom D, Arevalo JF. Short-term results of a single intravitreal bevacizumab (avastin) injection versus a single intravitreal triamcinoloneacetonide (kenacort) injection for the management of refractory noninfectious uveitic cystoid macular edema. Ocul Immunol Inflamm. 2009;17:423-30.*
16. *Soheilian M, Rabbanikhah Z, Ramezani A, Kiavash V, Yaseri M, Peyman GA. Intravitreal bevacizumab versus triamcinolone acetonide for refractory uveitic cystoid macular edema: a randomized pilot study. J Ocul Pharmacol Ther. 2010;26:199-206.*
17. *Rahimi M, Shahrzad SS, Banifatemi M, Rahimi M, Shahrzad SS. Comparison of intravitreal injection of bevacizumab and triamcinolone acetonide in the treatment of uveitic macular edema. Iran J Immunol. 2012;9:136-44.*
18. *Bae JH, Lee CS, Lee SC. Efficacy and safety of intravitreal bevacizumab compared with intravitreal and posterior sub-tenon triamcinoloneacetonide for treatment of uveitic cystoid macular edema. Retina. 2011;31:111-8.*
19. *Pleyer U, Klamann M, Laurent TJ, et al. Fast and successful management of intraocular inflammation with a single intravitreal dexamethasone implant. Ophthalmologica. 2014;*
20. *Tomkins-Netzer O, Taylor SR, Bar A, et al. Treatment with repeat dexamethasone implants results in long-term disease control in eyes with noninfectious uveitis. Ophthalmology 2014;121:1649-54.*
21. *Zarranz-Ventura J, Carreño E, Johnston RL, et al. Multicenter study of intravitreal dexamethasone implant in noninfectious uveitis: indications, outcomes, and reinjection frequency. Am J Ophthalmol. 2014;158:1136-45.*
22. *Taylor SR, Isa H, Joshi L, Lightman S. New developments in corticosteroid therapy for uveitis. Ophthalmologica. 2010;224(Suppl 1):46-53.*
23. *Patel CC, Mandava N, Oliver SC, Braverman R, Quiroz-Mercado H, Olson JL. Treatment of intractable posterior uveitis in pediatric patients with the fluocinolone acetonide intravitreal implant (Retisert). Retina. 2012;32:537-42.*
24. *Shen BY, Punjabi OS, Lowder CY, Sears JE, Singh RP. Early treatment response of fluocinolone (retisert) implantation in patients with uveitic macular edema: an optical coherence tomography study. Retina. 2013;33:873-7.*
25. *Arcinue CA, Cerón OM, Foster CS. A comparison between the fluocinolone acetonide (Retisert) and dexamethasone (Ozurdex) intravitreal implants in uveitis. J Ocul Pharmacol Ther. 2013;29:501-7.*