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CLINICAL STUDY

Lack of positive effect of intravitreal bevacizumab in central serous chorioretinopathy: meta-analysis and review

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Abstract

Purpose **To review and evaluate the effects of intravitreal bevacizumab injection (IVB) in centralserous chorioretinopathy (CSC) by meta-analysis.**

Patients and methods **Clinical controlled studies that evaluated the effect of IVB in CSC were identified through systematic searches of Embase, PubMed, and the Cochrane Central Register of Controlled Trials. Data on the best-corrected visual acuity (BCVA) in logMAR and central macular thickness (CMT) in μm at baseline and 6 months after IVB were extracted and compared with those treated by simple observation.**

Results **Four clinical controlled studies were included in the meta-analysis. The IVB injection group achieved better BCVA at a follow-up of 6 months. However, the analysis showed that there were no significant differences of BCVA at 6 months after injection between IVB group and the observation group (-0.02 logMAR, 95% CI -0.14 to 0.11, $P=0.80$). The analysis of the reduction in CMT revealed that the difference between groups was not statistically significant ($-8.37\,\mu$m, 95% CI -97.26 to 80.52, $P=0.85$). No report assessed severe complications or side effects of IVB in patients with CSC.**

Conclusions **Meta-analysis failed to verify the positive effect of IVB in CSC based on the epidemiological literature published to date.**

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Keywords: central serous chorioretinopathy; intravitreal bevacizumab injection; meta-analysis

Introduction

Central serous chorioretinopathy (CSC) is a common retinopathy with an uncertain pathology, characterized by serous detachment of the neurosensory retina.[1–4] The disorder is usually self-limited, although some patients are left with permanent visual impairment because of pigment epithelium and photoreceptor damage, especially in chronic CSC.[1,2,5,6] Hypotheses include abnormal alterations at the retinal pigment epithelium (RPE) level[2,3,7] and choroidal vascular hyperpermeability, as demonstrated on indocyanine green angiography.[7–9]

CSC has a high spontaneous remission rate, but there is evidence of the benefit of early treatment.[10–12] CSC with single, extrafoveal leaking point can be treated using focal photocoagulation to shorten the duration of symptoms without altering the final visual outcomes and the recurrent rate.[13–15] This method, however, has a significant adverse effect such as symptomatic scotomas, secondary choroidal neovascularization (CNV), and so on.[16,17] Recently, photodynamic therapy (PDT) with verteporfin has been tried as an alternative treatment to reduce underlying choroidal hyperpermeability and congestion.[18,19] The effect of the vascular modulation was successful with visual improvement in most of patients. However, there is a risk of complications, including RPE atrophy, choriocapillary hypoperfusion, and the development of CNV, especially with standard-dose PDT.[9,20] Half-dose PDT seems to be effective and safe, but its long-term efficacy is unknown.

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Bevacizumab (Avastin, Roche, Basel, Switzerland), a monoclonal antibody to vascular endothelial growth factor (VEGF), is a new treatment that exerts antipermeability effects in diabetic macular edema and CNV.[2,21] There have been several off-label clinical trials of intravitreal bevacizumab injection (IVB) in CSC.[1,2,13,22–25] Most showed positive results, with improved visual acuity and reduced subretinal fluid. However, these findings should be interpreted cautiously because of the self-limiting characteristics of CSC, which can show spontaneous improvement within months.[1,2,12,22–25]

Therefore, we performed a meta-analysis of the efficacy of IVB in terms of visual acuity and macular thickness to gain a better perspective regarding the therapeutic options in CSC.

Materials and methods

Search method

Three databases (PubMed, EMBASE, and Cochrane) were last searched on 20 August. 'Central serous chorioretinopathy', 'bevacizumab', and 'avastin' comprised the terms for the sensitive search. There was no restriction on study design but the eligible studies only covered those that were written in English. Duplicate articles were manually removed.

Inclusion and exclusion criteria

Published studies, regardless of sample size or study design, were included if the changes in the means and SDs from baseline to 6 months after injection were available for the best-corrected visual acuity (BCVA) in logMAR and central macular thickness (CMT) in μm. The follow-up period varied across the studies, and we chose to analyze the results at 6 months as this period was the most common to all of the included studies. The results of subjects who received IVB were extracted, and the treatment of controls was assigned as simple observation, PDT, or subthreshold laser. The primary outcomes were the change in BCVA and CMT from baseline after IVB. The mean difference and SD at the 6-month follow-up were calculated from the data in the included studies. Secondary outcomes were any reported complication of IVB in eyes with CSC. Case reports, interventional case series, and comments were reviewed but not subjected to analysis, and conference abstracts that had not been published were excluded (Table 1).

Quality assessment

The quality of the included randomized clinical trials (RCTs) was evaluated using the Delphi list.[26] Determined items were the following: randomization, allocation concealment, baseline similarity within groups, specified eligibility criteria, blinded outcome assessment, blinded care provider, blinded patient, point estimates and measure of variability presented, and intention-to-treat analysis.[26] Quality scores were calculated, with a response of 'yes' given one point for each item and 'not available' or 'no' given zero points. Total scores are presented in Table 2.

Statistical analysis

The meta-analysis was conducted using RevMan 5.1,[27] with application of a random effect model. Heterogeneity was examined using the I^2 statistic and was defined as significant at $I^2 < 50\%$. Squares indicate mean difference estimates, and lines extending from the squares reveal the associated 95% intervals in the forest plot display. Confidence intervals that do not intersect the vertical line at 0 indicate statistical significance at the 0.05 level.

Sensitivity analysis

In order to assess the influence of two non-RCTs, and Snellen and ETDRS to logMAR conversion included in the meta-analysis, these studies were excluded and the analysis was performed. Sensitivity analyses were undertaken using the following subgroups to assess reliability: (1) all studies including two RCTs and two non-RCTs, and (2) two RCTs with logMAR visual acuity.

Results

Result of search

The literature search yielded 155 articles, 50 from PubMed, 102 from EMBASE, and 3 from Cochrane Library. After excluding 138 ineligible articles because of various reasons such as duplicates from multiple databases, articles not matching the current topic, single case description, and different treatment modality, 17 studies were identified. There were 6 comparative studies, including 2 RCTs and 4 non-RCT studies (Table 3). The remaining 11 studies were interventional case series. After excluding 2 comparative studies because of the lack of data at 6 months of follow-up and the lack of observation group,[28,29] in total 112 patients were included in four comparative studies. Among those, 50 patients were in the treatment group with IVB as compared with 62 patients in the observation group.

Quality assessment

Nine criteria were used to judge the quality of two RCTs included in the meta-analysis. The two RTCs were of

Table 1 Characteristics of the excluded studies

Authors	*Year, place*	*Study type*	*Inclusion criteria*	*No. of eyes*	*Intervention*	*Follow-up period*	*Improvement in BCVA (logMAR)*	*Reduction in CMT (μm)*	*Adverse effects*	*Conclusion*
Entezari *et al*[43]	2012, Iran	Prospective interventional case series	Refractory CSC >1 year	5	1.25 mg IVB	6 mon	0.60 to 0.24	370 to 210	NA	Effective in refractory CSC
Jamil *et al*[42]	2012, Pakistan	Prospective intervention case series	CSC <6 mon and >6 mon	43	1.25 mg IVB repeated at 4 weeks if SRF present	6 mon	Decimal 0.25 to 0.70	557 to 286	NA	IVB results visual improvement and reduced neurosensory detachment
Lim and Kim[22]	2011, Korea	Prospective interventional case series	CSC >3 mon	40	1.25 mg IVB, repeated at 6 weeks if SRF present	>12 mon	Improved group: 0.25 to 0.09, Persistent group 0.25 to 0.2	Improved group 432 to 201, Persistent group 432 to 377	NA	82.5% showed complete resolution of SRF within 3 months IVB is efficacious
Lee and Adelman[25]	2011, USA	Retrospective case series	Recurrent	3	1.5 mg IVB, repeated at every 4 weeks if SRF present	Case 1: 4 mon, Case 2: 6 mon, Case 3: 9 mon	(1) 0.3 to 0 (2) 0.3 to 0.1 (3) 0.3 to 0	(1) 500 to 162 (2) 344 to 187 (3) 320 to 405	Thick CMT persistent in case 3	Effective treatment option for recurrent CSC
Inoue *et al*[24]	2011, Japan	Prospective interventional case series	Chronic CSC >6 mon or recurrent type	5	1.25 mg IVB, repeated at 4 weeks if SRF present	12 mon	0.23 to 0.17	323 to 171	None	Well tolerated in maintaining vision and reducing SRF
Li and Zhang[3]	2010, China	Case series	CSC >6 mon	2	2.5mgIVB	6 mon	(1) 0.4 to 1.0 (2) 0.5 to 1.0	NA	None	Promising results
Mehany *et al*[41]	2010, Egypt	Prospective interventional case series	Group 1: acute CSC Group 2: CSC >6 mon or recurrent type	20	1.25 mg IVB repeated injection	6 mon	Group 1 0.48 to 0.18 Group 2 0.60 to 0.30	486 to 272	Subconj hemo	Promising results
Lim *et al*[13]	2010, Korea	Retrospective case series	CSC >3 mon and recurrent type	6	1.25 mg IVB	3 mon	ETDRS letters 40.8 to 53.3	331.5 to 164	NA	Effective, but recurrence after 4 to 5 months after IVB in 4 of 6 patients
Seong *et al*[1]	2009, Korea	Retrospective interventional case series	Acute CSC <6 mon	10	1.25 mg IVB	6 mon	0.32 to 0.04	NA	None	Promising results
Schaal *et al*[23]	2009, Germany	Interventional case series	Chronic CSC	12	2.5 mg IVB, repeated at 6–8 weeks if SRF present	6 mon	0.58 to 0.42	304.5 to 218.8	NA	Promising therapeutic option in the treatment of chronic CSC
Torres-Soriano *et al*[2]	2008, Mexico	Interventional pilot study	CSC >3 mon, recurred, or acute with severe symptoms	5	2.5 mg IVB	6 mon	Description by case, 4 cases improved to Snellen 20/20, one case 20/40 to 20/25	Description of 2 cases: 394 to 170, 428 to 210	NA	Possibly effective

Abbreviations: BCVA, best-corrected visual acuity; CMT, central macular thickness; CSC, central serous chorioretinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; IVB, intravitreal bevacizumab injection; mon, months; NA, not available; SRF, subretinal fluid.

reasonable to good quality, and the mean quality score was 55.6%.

Characteristics of studies

The differences in the baseline BCVA, CMT, and demographics between the IVB and control groups were not significant in each of the included studies. However, the clinical heterogeneity among the included studies was considerable in several areas. As for the inclusion criteria, the two studies by Lim *et al*[30] and Aydin[31] recruited patients with acute CSC of <3-month duration, whereas the other studies included those with CSC of >3 months. The included studies used the different control

Table 2 Quality assessment of included randomized clinical trial studies based on Delphi list

Study	*Randomization*	*Treatment allocation concealment*	*Baseline group similarity*	*Eligibility criteria specified*	*Blinded outcome assessor*	*Care provider blinded*	*Patient blinded*	*Point estimates presented*	*Intention-to-treat analysis*	*Total score*
Artunay *et al*[32]	Yes	No	Yes	Yes	NA	No	No	Yes	Yes	5
Lim *et al*[30]	Yes	No	Yes	Yes	NA	No	No	Yes	Yes	5

Abbreviation: NA, not available.

groups: the three studies by Artunay *et al*,[32] Lim *et al*,[30] and Aydin[31] used patients with observation, whereas the other studies by Semeraro *et al*[29] and Lee *et al*[28] used only those treated with PDT. Both the observation group and a group treated with a subthreshold laser were used as controls in the study by Koss *et al*.[33] Moreover, four studies had consistent treatment arms comparing 1.25 mg/0.05 ml of IVB to the control group, whereas Artunay *et al*[32] performed IVB with 2.5 mg/1.0 ml. Furthermore, Artunay *et al*,[32] Lim *et al*,[30] and Aydin[31] simply evaluated the effect of IVB after a single injection, whereas the others allowed repeated treatment with the same modality, guided by BCVA, OCT, and fluorescein angiography (FA).

Visual acuity

Figure 1 shows the forest plot of the BCVA results of IVB and the observation group as a control. Examination of the forest plot demonstrated that, with the exception of the results shown by Aydin,[31] the IVB injection group achieved better BCVA at a follow-up of 6 months. Meta-analysis of these data revealed no statistically significant differences between the two groups (-0.02 logMAR, 95% CI -0.14 to 0.11, $P=0.80$). Because heterogeneity ($I^2=68\%$) was substantial, a random effects model was used to present the data.

Central macular thickness

The forest plot showed that the IVB group was associated with more reduction in CMT than the control group. However, analysis of these data revealed that the difference between groups was not statistically significant ($-8.37\,\mu$m, 95% CI -97.26 to 80.52, $P=0.85$; Figure 2).

Comparison among different treatment modalities was not possible because of the small number of available data on the subject.

Sensitivity analysis

Sensitivity analyses of primary outcomes excluding two non-RCTs resulted in similar outcomes. The two non-RCTs included in this meta-analysis did not have an important impact: (1) (-0.02 logMAR, 95% CI -0.14 to 0.11, $P=0.80$) and (2) (-0.09 logMAR, 95% CI -0.20 to 0.01, $P=0.09$).

Adverse effects

There was no report of complications or side effects of IVB in patients with CSC in either the included or excluded studies except mild subconjuctival hemorrhage at the injection site.

Discussion

CSC is a self-limiting disease, but it can cause permanent photoreceptor damage or RPE atrophy that leads to visual impairment.[34] The greater the understanding of the pathophysiology of CSC with advances in imaging, the more doubts about the so-called 'benign' nature of CSC. Several treatment modalities have been tried. Treatment with acetazolamide might shorten the duration of the disease without influencing the final visual acuity or recurrence rate.[35] Other medical treatments such as mifepristone, aspirin, finasteride, and propanolol have been reported with good results but require well-designed randomized controlled study to evaluate their efficacy and safety.[36–39] One of the traditional treatments is focal laser photocoagulation, although its application is limited because of possible scotoma or secondary CNV when the RPE leak is close to the fovea.[14] Some authors reported that laser photocoagulation was effective in shortening the duration of CSC and reducing the recurrence rate, whereas others reported no definite advantage in terms of the final vision or recurrence.[2] PDT is another option for treatment of CSC, as choroidal hyperpermeability has been suggested as the underlying pathology, but foveal atrophy was reported as a possible complication and PDT is expensive.[19,40]

Recently, anti-VEGF antibody has been used in CSC as an off-label method.[1–3,22–24,28,30,32,33,41–43] Bevacizumab is a recombinant humanized full-length monoclonal antibody of VEGF that penetrates the retina and is transported into the photoreceptor outer segments, RPE,

Table 3 Characteristics of the reviewed comparative studies

Authors	*Year, place*	*Study type*	*Inclusion criteria*	*Study groups (no. of eyes)*	*Follow-up period*	*BCVA (logMAR)*	*CMT (μm)*	*Adverse effects*	*Conclusion of the study*
Artunay *et al*[32]	2010, Turkey	Prospective randomized controlled study	>3 mon	IVB group (15) Control (15)	6 mon	IVB: 0.32 to 0.03 Control: 0.29 to 0.14	IVB: 485 to 174 Control: 480 to 297	None	Single IVB 2.5 mg(0.1 ml) led to a rapid morphlogic and functional restitiution without relapse or complication during 6-month period after injection
Lim *et al*[30]	2010, Korea	Prospective randomized comparative study	<3 mon	IVB group (12) Control (12)	6 mon	IVB: 0.23 to 0.02 Control: 0.20 to 0.02	IVB: 431 to 207 Control: 442 to 187	None	In patients with acute CSC, IVB showed no positive or negative effect in terms of earlier remission, functional results, or anatomical results
Lee *et al*[28]	2011, Korea	Retrospective nonrandomized comparative case series	>6 mon or recurred	IVB group (16) PDT group (13)	6 mon	IVB: 0.32 to 0.18 PDT: 0.37 to 0.19	IVB: 290 to 219 PDT: 332 to 171	Foveal thinning in PDT group	IVB is effective as PDT in treating chronic CSC, but mean visual acuity increased significantly more in PDT group
Semeraro *et al*[29]	2012, Italy	Prospective comparative case series	>3 mon	IVB group (12) PDT group (10)	9 mon without (6 mon)	IVB: 0.7 to 0.24[a] PDT: 0.5 to 0.3[a]	IVB: 348 to218 PDT: 361 to 247	None	IVB may be treatment option for chronic CSC
Koss *et al*[33]	2012, Germany	Prospective comparative nonrandomized controlled study	>3 mon	Laser group (16) IVB group (10) Control (26)	10 mon including (6 mon)	(1) 0.19 to 0.09[a] (2) 0.22 to 0.25[a] (3) 0.17 to 0.20[a]	(1) 419 to 325 (2) 393 to 355 (3) 388 to 414	None	Laser group showed superior fluid resorption, and BCVA at 6 mon follow-up compared with IVB and control
Aydin[31]	2012, Turkey	Prospective comparative case series	>6 weeks and <3 mon	IVB group (13) Control (9)	6 mon	IVB: 0.41 to 0.14[b] Control: 0.60 to 0.17[b]	IVB: 414 to 198 Control: 510 to 205	None	IVB-injected patients demonstrated prompt improvements in visual acuity rather than control within 3 months. But, there was no significant difference between the 2 groups at 6 months

Abbreviations: BCVA, best-corrected visual acuity; CMT, central macular thickness; CSC, central serous chorioretinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; IVB, intravitreal bevacizumab injection; PDT, photodynamic therapy.
[a]ETDRS letters conversion to logMAR.
[b]Decimal conversion to logMAR.

and choroid after intravitreal injection.[44] The half-life of bevacizumab in the vitreous is 5.6 days, and it remains in the eye for 4 to 6 weeks.[45] Many studies of other macular diseases have reported that the CMT starts decreasing or stabilizes in most eyes at 3–6 weeks.[45–48] The mechanism of IVB in the resolution of subretinal fluid in CSC is unknown, but might involve effects on choroidal vascular hyperpermeability.[2,3,13]

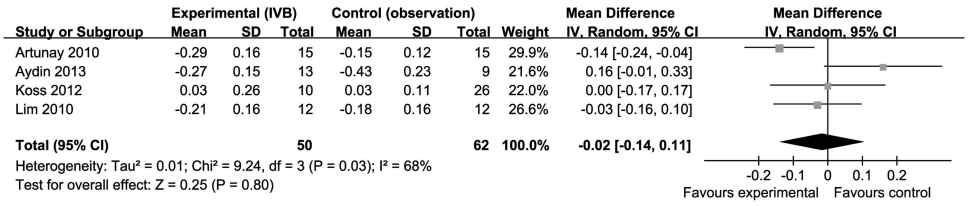

Figure 1 Forest plot showing the mean differences in BCVA in logMAR, with 95% confidence intervals, of experimental (IVB group) compared with the control group (observation) at 6 months. The differences were not significant.

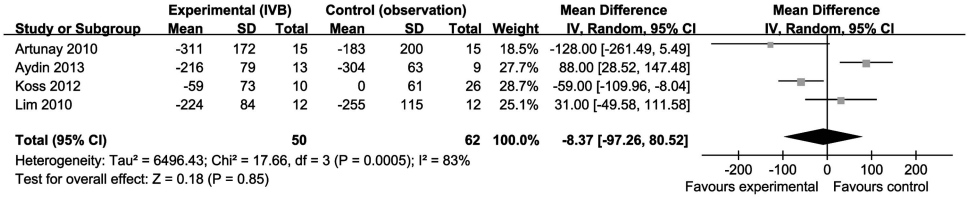

Figure 2 Forest plot of the mean differences in CMT in μm, with 95% confidence intervals, of experimental (IVB group) compared with the control group (observation) at 6 months. The differences were not significant.

Considering the self-limiting characteristics of CSC, usually within 3–6 months, many of the clinical case studies selected patients with CSC of >3 months as subjects for IVB. Most case series reported no specific complications, although there is always some risk of postinjection endophthalmitis.[49] Most studies reported that IVB might be effective in terms of improving visual acuity and reducing CMT without significant complications and can be considered an optional intervention,[1,2,23,24,28,32,33] but these conclusions should be interpreted cautiously owing to the self-limiting nature of acute and even in chronic CSC. Moreover, it should be noted that the aqueous humor and plasma levels of VEGF were not significantly increased in patients with CSC compared with the healthy control group.[50]

Four studies were included in this meta-analysis. They compared the effects of IVB with simple observation. Nonrandomized studies were included, although it is usually better to exclude these from meta-analyses, because we believe that BCVA and CMT are not influenced by randomization. In this meta-analysis, the visual acuity at 6 months after injection was not significantly improved in the IVB group compared with simple observation, and the CMT was also not significantly reduced in the IVB group. Thus, a beneficial role of IVB in treating chronic or acute CSC can be discouraging.

Comparison with other treatment modalities was less valuable because of the relative lack of studies, and the role of IVB remains elusive. Semeraro *et al*[29] reported that IVB group showed greater improvement in the mean BCVA compared with low-fluence PDT (300 mW/cm^2 for 83 s, light dose 25 J/cm^2) group at 9-month follow-up, although it was not statistically different. In contrast, it was reported by Lee *et al*[28] that the mean BCVA was increased significantly more in standard PDT-treated group. Foveal thinning occurred more frequently in PDT group than in IVB group in both studies. Subthreshold laser photocoagulation (810 nm infrared diode) resulted superior to the IVB for resolution of SRF and BCVA improvement at 6 and 10 months after treatment in the study by Koss *et al*.[33]

Although our study confirmed the lack of efficacy of IVB for CSC over a 6-month period, the outcome of this treatment is still unknown. Despite the considerable available literature providing the possible efficacy of IVB for CSC, the majority of studies was simple interventional case series, and was not randomized. As a result, small sample sizes made it difficult to detect differences between the treatments and the observation. The second limitation is that the clinical heterogeneity among comparative studies was considerable in several areas, including inconsistency in inclusion criteria, and treatment protocols. The acute and chronic CSC were all subjected to the meta-analysis together. It would have been more meaningful meta-analysis to differentiate them, considering there might be inherent differences in the nature of acute and chronic CSC. However, chroidal vascular hyperpermeability is considered to be fundamental mechanisms for acute and chronic CSC, and the current treatment concept such as PDT or IVB is focused on modulating hyperpermeability in choroid. There has been language bias as the eligible studies only covered those that were written in English. Despite these limitations, this analysis makes an important

contribution to the field because this study was the first meta-analysis to explore the use of intravitreal bevacizumab for CSC.

In conclusion, meta-analysis failed to verify the positive effect of IVB in CSC based on the epidemiological literature published to date. In the future, more studies using larger scales and better methodologies will help to clarify the uncertain relationship between CSC and IVB.

Summary

What was known before:

- Anti-VEGF antibody has been used in CSC as an off-label method with positive results.

What this study adds:

- The positive effect of IVB in CSC, based on the epidemiological literature published to date, could not be verified.

Conflict of interest

The authors declare no conflict of interest.

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Author Contributions

Design of the study (Y-RC and KL); conduct of the study (Y-RC and EJS); preparation of the manuscript (Y-RC and KL); review and approval of the manuscript (KL and HML).

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