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REVIEW

Photodynamic therapy and anti-vascular endothelial growth factor for acute central serous chorioretinopathy: a systematic review and meta-analysis

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Abstract

This systematic review aims to update current evidence on the efficacy and safety of photodynamic therapy (PDT) and anti-vascular endothelial growth factor (anti-VEGF) injections for acute central serous chorioretinopathy (CSC). A comprehensive literature search was conducted in PubMed, EMBASE, and Cochrane Library. Studies comparing (1) PDT versus placebo, (2) anti-VEGF versus placebo, and (3) PDT versus anti-VEGF were included and meta-analyzes were performed when appropriate. Ocular and systemic adverse effects were also summarized. Literature search yielded six comparative studies, among which five were included for this review. Meta-analysis with three studies indicated that eyes treated with PDT achieved better best-corrected visual acuity (BCVA) and central macular thickness (CMT) than the placebo group throughout a follow-up of 12 months. Meta-analysis with another two studies comparing anti-VEGF injections and placebo showed that BCVA at first month was better in anti-VEGF group than in placebo group, though the differences of BCVA and CMT no longer existed at 3 and 6 months after injection. There was no report directly comparing PDT and anti-VEGF for acute CSC. No severe complications was reported in included studies. In this review, current evidence suggested that early treatment of acute CSC by PDT is valuable in improving visual acuity, reducing subretinal fluid, and maintaining long term effectiveness. Anti-VEGF injection could shorten the duration of symptoms and accelerate visual improvement at early stage of disease. Direct comparison between these two treatment will be needed in the future.

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Introduction

Central serous chorioretinopathy (CSC) is characterized by serous detachment of the neurosensory retina at the macula with or without pigment epithelial detachment, which typically affects young and middle aged adults. The pathologenesis is believed to involve the hyperperfusion of choroid and impairment of retinal pigment epithelium barrier. Patients may experience decreased vision, altered color vision, visual distorsion, or central scotoma.

The natural history of CSC in most patients is self-limiting.[1] The subretinal fluid may disappear in a couple of months without any treatment, and the prognosis is often good. Spontaneous resolution, however, does not always happen within the first 3 months of disease. Cases which do not resolve spontaneously might turn into chronic course of CSC. Gass *et al*[2] demonstrated that 5% of patients may experience severe visual disturbances/impariment. In the first year, the recurrent rate is ~30–50%.[3] So treatment is needed in these chronic cases to prevent progressive pigment epithelial and photoreceptor damage and irreversible visual impairment.[2,4,5] Current strategies for treating chronic or recurrent CSC include fluorescein angiography guided laser photocoagulation, photodynamic therapy (PDT), and anti-vascular endothelial growth factor (anti-VEGF) therapy.[5–8]

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Whether the condition warrants an early intervention within 3 months of onset remains controversial. Some studies suggested that some patients might experience visual loss after spontaneous resolution and prompt treatment in acute CSC could result in better visual outcomes.[9–11] Others indicated that early treatment did not make significant difference in long-term visual acuity.[4,12,13] Considering the self-limiting nature of CSC, treatment attempts for acute CSC should pay special attention on safety. Laser photocoagulation targeting extrafoveal leaking point might induce paracentral scotoma, and thus less considered for acute CSC.[14,15] PDT and intravitreal anti-VEGF injection, which are generally agreed on their safety profile, have been used in the treatment of acute CSC.[16,17] Several studies have demonstrated that PDT applied to the regions of documented choroidal vascular hyperpermeability on ICGA is effective for the treatment of CSC by inducing local choroidal hypoperfusion.[18–21] Moreover, vascular endothelial growth factor (VEGF) has been implicated as the major factor responsible for increased vascular permeability.[22–24] In acute CSC, the efficacy of PDT or anti-VEGF treatment has been observed by a few studies.[10,17,25,26] However, other studies[13] made different conclusions that the efficacy of PDT and anti-VEGF for acute CSC is neither statistically nor clinically significant.

This study aims to systematically review and meta-analyze published studies on PDT and anti-VEGF therapy for acute CSC, and guide future clinical practice.

Methods

Search strategy

Three databases (PubMed, EMBASE, and Cochrane Library) were last searched on September, 2014. In conducting the search in PubMed, EMBASE, three domains of terms were searched: (1) PDT or equivalents (eg, photodymic therapy, verteporfin, and visudyne), (2) anti-VEGF or equivalents (eg, ranibizumab, bevacizumab, afflibercept, and conbercept), and (3) CSC or equivalents (eg, central sereous chorioretinopathy). The results from each domain were then combined with OR. In Cochrane Library, CSC or equivalents was used in search. The details of search methodologies are illustrated in Appendix. The selected paper had been written in English, and no restrictions were imposed on study design. All potentially related articles were retrieved and imported into EndNote X7(Thomson Reuters, New York, NY, USA), where duplicate studies were manually removed.

Inclusion and exclusion criteria

Published comparative studies, whether randomized controlled trials (RCTs) or non-RCT studies, were included if they compared (1) PDT versus placebo; (2) anti-VEGF versus placebo; or (3) PDT versus anti-VEGF in the treatment of acute CSC eyes without previous intervention. The selected studies should include one or more of the following results at months 1, 3, 6, 12 or longer observation time point: best-corrected visual acuity (BCVA), central macular thickness (CMT), and ocular or systemic adverse events. Two authors independently reviewed the titles and abstracts of retrieved articles, and determined whether they met inclusion criteria. Full texts were read as necessary. Disagreement and inconsistencies were discussed and resolved by discussion and consensus.

Quality assessment

Study quality was evaluated and assessed using the tool described by Jadad scores (5-point). Jadad scores include the following criteria: randomization, double blinding, and description of withdraws and dropouts. Moreover, the additional criteria are (1) the description of randomization method was appropriate, and (2) the description of double blinding method was appropriate. The studies scored 1 point for each criterion met.[27]

Statistical analyzes

All RCTs and non-RCT studies with balanced baseline measurements were considered for meta-analysis. We performed all meta-analyzes using the Review Manager (RevMan) software, version 5.3.3(Cochrane Collaboration, Oxford, UK). Data from the articles were combined using a fixed-effects and continuous variable pattern. In the meta-analysis, the effect sizes of each study were presented as mean difference with 95% confidence intervals (CI). If the 95% CI of weighted mean difference crossed zero, the pooled effect sizes were considered statistically insignificant. According to baseline characteristics and estimated statistical heterogeneity, I-square (I^2) statistic was to examine and evaluate the clinical statistical heterogeneity among studies ($I^2 \leq 40$, insignificant heterogeneity). Sensitivity analysis was assessed by sequentially omitting one study. Because of the limited number studies, potential publication bias was not analyzed.

Results

Results of literature search

The literature search yielded 434 articles, 163 from PubMed, 217 from EMBASE, and 54 from Cochrane Library. By removing 171 duplicated articles, 263 articles

without duplicates were yielded. Then 230 ineligible articles, 12 comments and author replies, 6 reviews and 1 case report were excluded, producing 14 relevant study reports (Figure 1). After excluding eight non-comparative case series,[10,16,28–33] the remaining six comparative studies, including four RCTs [9,11,13,34] and two non-RCTs,[25,26] were included for study (Table 1).

Study characteristics

Three comparative studies, including two RCTs and one non-RCT study, compared PDT and placebo, and the other three, including two RCTs and one non-RCT study, compared anti-VEGF injections and placebo. There was no study directly comparing PDT and anti-VEGF therapy. The characteristics of the included six study was displayed in Table 1. Six studies[9,11,13,25,26,34] differed in regions, sample sizes, and the proportion of patient allocation in the treatment and control groups. In all three studies which compared PDT and placebo, PDT groups were treated with 50% of standard dosage of verteporfin. Among the three studies comparing anti-VEGF and placebo, two RCTs[9,13] used standard injection dosage (1.25 mg bevacizumab or 0.5 mg ranibizumab), and in one non-RCT study by Aydin *et al*[26] bevacizumab (2.0 mg) was injected. Because of non-standard dosing, imbalanced baseline, and distinct data analyzing method, the study by Aydin *et al* was excluded from further meta-analysis.

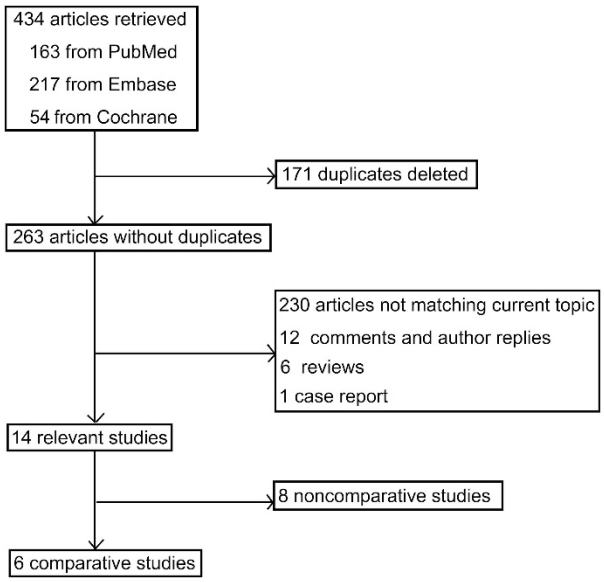

Figure 1 Flow diagram showing the process of study selection from 434 retrieved articles which yielded 6 studies ready to be evaluated for meta-analysis.

Comparison of the photodynamic therapy and placebo

The three studies[9,11,34] which compared functional and anatomic repairs between the PDT (50% dose of verteporfin) and placebo did not show significant statistical or clinical heterogeneity. Meta-analysis demonstrated significant benefits of PDT through 12 months of observation. The weighted mean difference (95% CI) of BCVA (logMAR) and CMT (μm) between PDT and placebo group at month 1, 3, and 12 were − 0.01 (−0.06, 0.03), − 0.07 (−0.12, − 0.02), − 0.09 (−0.15, − 0.03), and − 119 (−175, − 62), − 121 (−182, − 59), − 72 (−111, − 33), respectively (Figures 2 and 3). Sensitivity analysis indicated that no studies substantially influenced the final results.

Table 1 Characteristics of comparative studies

Author	*Year*	*Origin*	*Study design*	*Follow-up (months)*	*Baseline characteristics*			*Arms of intervention*			*Jadad score*
					Mean age	*Previous therapy*	*Duration of symptoms*	*No. of Eyes*	*Intervention*[a]	*Dose*	
Chan *et al*[11]	2008	Hong Kong	RCT	12	41.0 ± 6.7	No	<3 months	39	PDT	50%	5
								19	placebo	NA	
Wu *et al*[34]	2011	Hong Kong	RCT	12	41.9 ± 6.4	No	<3 months	24	PDT	50%	5
								10	placebo	NA	
Kim *et al*[25]	2014	Korea	Non-RCT	12	42.9	No	4.9 ± 3.4 weeks (<3 months)	10	PDT	50%	0
								11	placebo	NA	
Lim *et al*[13]	2010	Korea	RCT	6	43.2 ± 9.0	No	<3 months	12	IVB	1.25 mg	3
								12	placebo	NA	
Kim *et al*[9]	2013	Korea	RCT	6	NA	No	<3 months	20	IVR	0.5 mg	2
								20	placebo	NA	
Aydin *et al*[26]	2013	Turkey	Non-RCT	6	NA	NA	<3 months	13	IVB	2.0 mg	0
								9	placebo	NA	

Abbreviations: IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; NA, not available or applicable; PDT, photodynamic therapy; RCT, randomized controlled trial. [a]All interventions are single-procedure conductions.

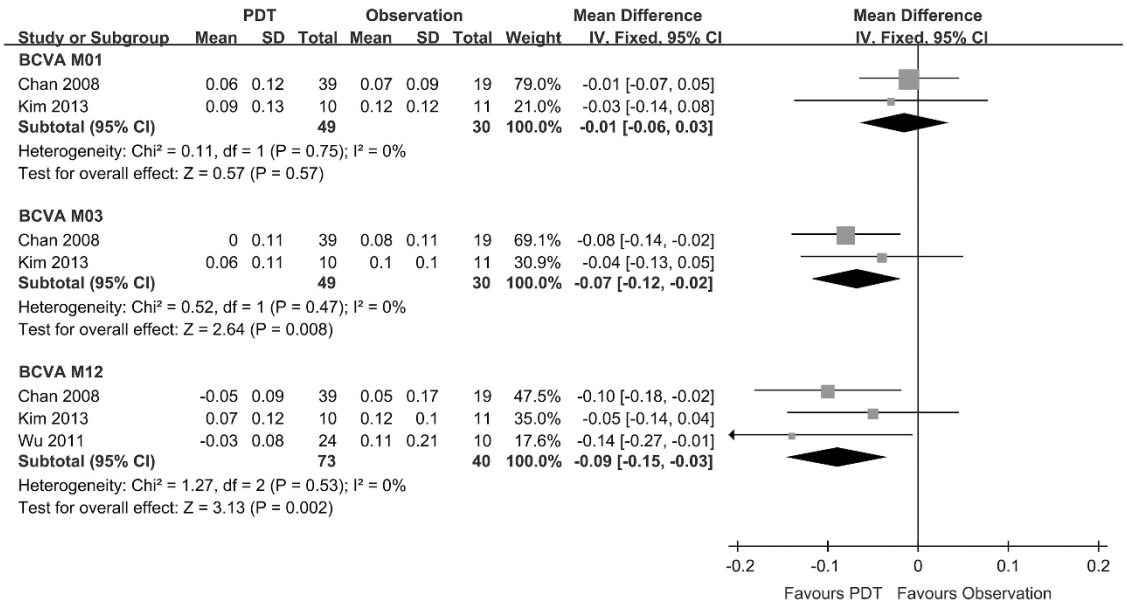

Figure 2 Forest plot of BCVA in the treatment at 1, 3, and 12 months between the PDT and control group.

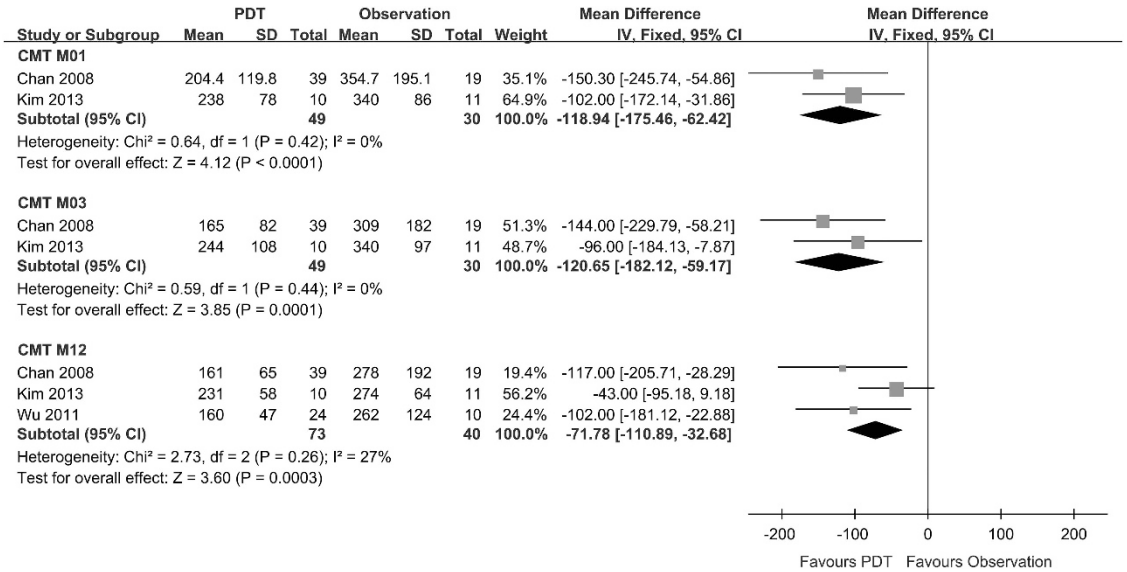

Figure 3 Forest plot of CMT in the treatment at 1, 3, and 12 months between the PDT and control group.

Comparison of the intravitreal anti-VEGF injection and placebo

The 2 RCTs which compared anti-VEGF injections and placebo did not show significant statistical or clinical heterogeneity.[9,13] Meta-analysis revealed early (month 1) visual benefits of anti-VEGF therapy, whereas the benefits tended to shrink quickly over time. The weighted mean difference (95% CI) of BCVA (logMAR) and CMT (μm) between anti-VEGF and placebo group at months 1, 3, and 6 were − 0.07 (−0.14, − 0.01), 0.01 (−0.04, 0.06), 0.01 (−0.05, 0.07), and − 49 (−108, 10), − 8 (−68, 53), 0 (−70, 70), respectively (Figures 4 and 5).

Safety

Except for mild subconjunctival hemorrhage at injection site, no severe ocular or systematic complication was reported to be associated with intravitreal anti-VEGF injections in either the included or excluded studies. PDT was also considered to be safe and no adverse event was reported.

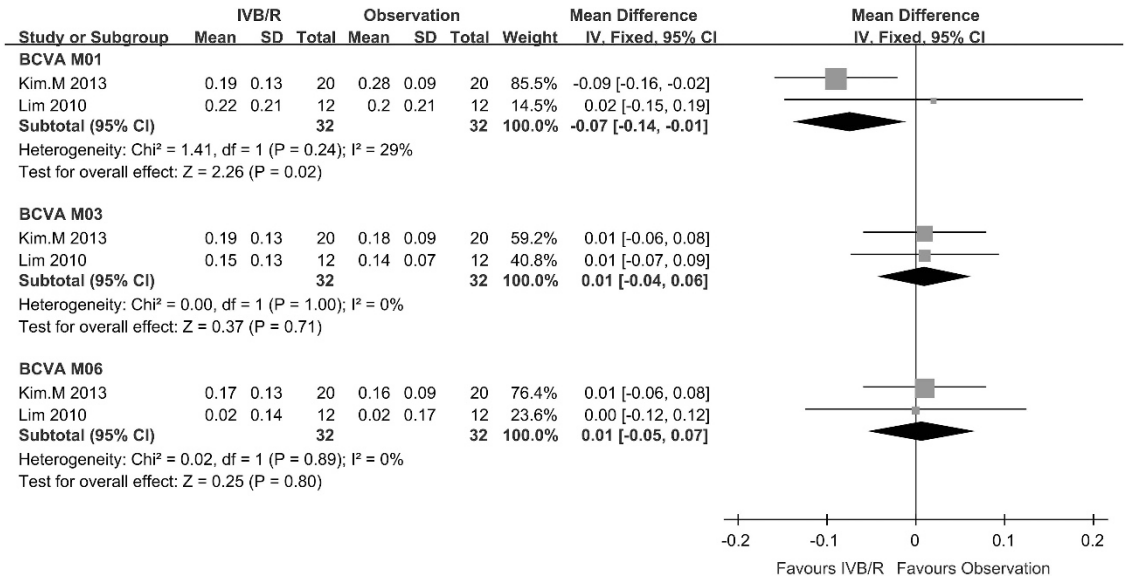

Figure 4 Forest plot of BCVA in the treatment at 1, 3, and 12 months between the IVR/B and control group.

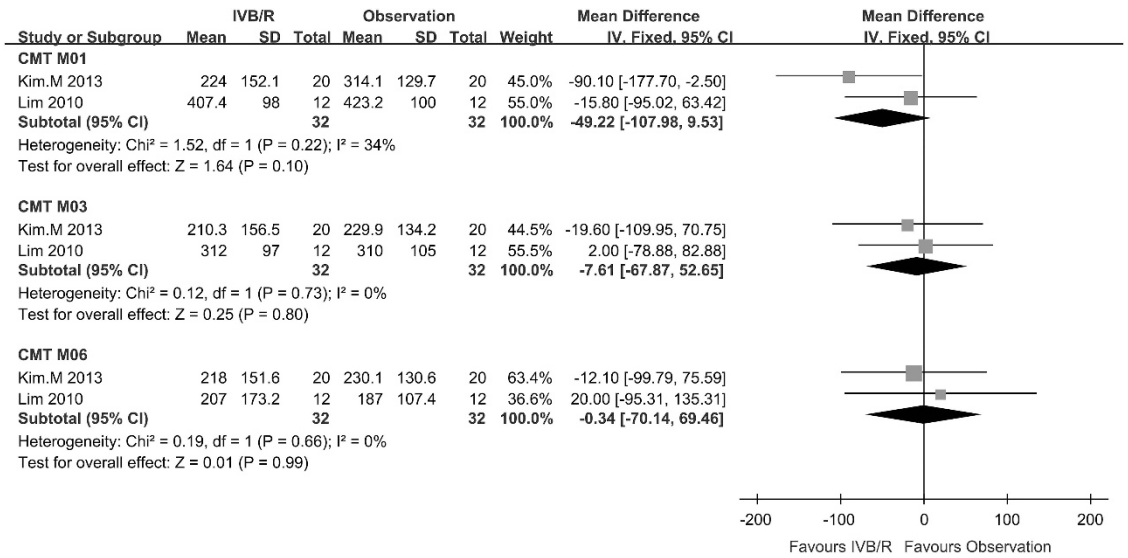

Figure 5 Forest plot of CMT in the treatment at 1, 3, and 12 months between the IVR/B and control group.

Discussion

Based on the self-limiting nature of CSC, the generally agreed rule for CSC management used to be that an at least 3-month period of observation should be given first to patients with acute episodes of CSC before considering treatment. Accumulating evidences are challenging this notion. Our systemic review and meta-analysis revealed that early treatment of acute CSC with PDT is associated with better long term visual and anatomical outcomes. Anti-VEGF injections might also help in accelerating visual recovery though significant difference was not observed in long term follow-up.

This means that the patients will suffer blurred vision, metamorphopsia, micropsia, dyschromatopsia, hypermetropization, and central scotoma, as well as loss of contrast sensitivity and increasing hyperopia until spontaneous resolution occurs. We demonstrate that acute CSC may be treated in patients who often desire rapid rehabilitation of the disease and vision. We should consider the effectiveness of treatment to improve vision, shortening the duration of symptoms, reducing recurrence, and even a more detailed evaluation of visual function such as contrast sensitivity, retinal sensitivity and so on.

Although thermal laser photocoagulation applied to extrafoveal leaking point has been shown to shorten the duration of symptoms, it is not without complications such as central scotoma, secondary choroidal neovascularization (CNV), foveal leakage, and so on. Therefore, thermal laser photocoagulation can not be widely used to the treatment of CSC. It has been proved that standard-dose PDT is useful and effective in the treatment of CSC. Nevertheless, potential side effects may occur after treatment, such as RPE atrophy, macular ischemia, even secondary CNV, and so on. Restricting the dosage of PDT for CSC may minimize complications, rapidly reduce the choroidal hyperpermeability and prompt resolution of subretinal fluid. For its advantage, reducing the dosage of PDT has been already applied for chronic CSC.[20,28,35–38]

Currently, there are many research on the treatment of acute CSC, most studies are non-RCTs. Two RCTs and one non-RCT comparative studies were included for the comparison between the PDT and observation groups. There was no significant difference in baseline between the treatment and observation groups for the non-RCT study. According to meta-analysis, patients with acute CSC treated with half-dose PDT achieved significant difference in the improvement of BCVA and CMT recovery than the observation group.

Recently, anti-VEGF antibody has been used in CSC as an effective and safe treatment option.[9] Bevacizumab, a recombinant humanized full-length monoclonal antibody of VEGF, could penetrate the reretina and is transported into the photoreceptor outer segments, RPE, and choroid after intravitreal injection. Many studies have reported that intravitreal bevacizumab was associated with visual acuity improvement and reduced neurosensory detachment without adverse events in patients with CSC. Ranibizumab may have potentially better retinal penetration than bevacizumab because of its smaller molecular size and higher binding affinity for VEGF.[9,39]

According to recent research, two RCTs reported intravitreal bevacizumab/ranibizumab injection in the treatment of acute CSC. Meta-analysis of 6-month studies showed patients for acute CSC treated with injection gained significantly better BCVA than the observation group at the 1-month follow-up. However, there are no significant difference in the BVCA or CMT recovery between the treatment and observation groups over time. The outcomes may be related to the small number of cases, and the short follow-up period. More objective parameters should be needed to assess the visual functional changes, such as contrast sensitivity, retinal sensitivity, and so on.

In conclusion, early and prompt treatment should be advocated in acute CSC patients. The prefered therapy is PDT, which is likely to result in better functional and anatomical outcomes in long term observation. Though anti-VEGF injections accelerated early restoration of vision and quick absorption of subretinal fluid, the benefits no longer existed at month 3 and thereafter. Future studies should include large number of subjects with a long period of follow-up. The involvement of new functional index such as contrast sensitivity, microperimetry and electrophysiological measurements might also help in redefining 'acute CSC', determining optimal treatment time point, and evaluating individual prognosis.

Summary

What was known before

- Treatment is not always applied and chosen in the course of acute central serous chorioretinopathy (CSC).
- Few and little evidence could verify the positive effect of intravitreal bevacizumab in CSC (acute or chronic).

What this study adds

- In acute CSC, treatment is needed and effective.
- Photodynamic therapy is valuable in improving visual acuity, reducing subretinal fluid, and maintaining long term effectiveness; but anti-vascular endothelial growth factor injection only shorten the duration of symptoms.

Conflict of interest

The authors declare no conflict of interest.

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Appendix

Appendix Search Strategies

The PubMed and Embase Search Strategies
#1 central serous chorioretinopathy
#2 photodynamic therapy
#3 verteporfin
#4 visudyne
#5 ranibizumab
#6 bevacizumab
#7 avastin
#8 anti-VEGF OR anti-vascular endothelial growth factor
#9 intravitreal injection
#10 #2 OR #3 OR #4
#11 #5 OR #6 OR #7 OR #8 OR #9
#12 #1 AND #10
#13 #1 AND #11
#14 #12 OR #13
The Cochrane Library Search Strategy
central serous chorioretinopathy