

# Intravitreal Bevacizumab for Pseudophakic Cystoid Macular Edema; a Systematic Review

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Cystoid macular edema (CME) is a major cause of decreased vision after complicated or uncomplicated cataract surgery. This paper reviews the use of intravitreal bevacizumab (IVB) injection for treatment of pseudophakic CME. In a literature search of all articles available on Medline and Scopus databases, 11 studies including one prospective and 4 retrospective studies, 4 case reports, one letter to editor and one review article were identified. All articles except one, reported the use of IVB for chronic CME unresponsive to at least one conventional treatment modality. The level of evidence for all studies was categorized as low or very low. Although intravitreal bevacizumab might be effective for many cases of pseudophakic CME, its use should be reserved for eyes unresponsive to conventional treatment modalities.

**Keywords:** Cystoid Macular Edema; Cataract Surgery; Intravitreal Injection; Bevacizumab Anti Vascular Endothelial Growth Factor

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## INTRODUCTION

Cystoid macular edema (CME) is a common cause of decreased vision following complicated or uncomplicated cataract surgery. It may occur angiographically after uneventful intracapsular and extracapsular cataract surgery in up to 60% and 30% of cases respectively; however, the incidence of clinically significant CME is much lower (0.1-13%).<sup>1-4</sup> The rate of angiographic and clinical CME after phacoemulsification cataract surgery is lower (approximately 20% and 1-2%, respectively).<sup>4,5</sup>

CME usually resolves spontaneously in about 90% of eyes and only a small subset of patients suffer permanent visual morbidity.<sup>4,6</sup> Considering the large number of patients

undergoing cataract surgery, this small percentage of patients represents a population large enough to drive ongoing research to identify appropriate treatment strategies.<sup>4</sup> Various treatment modalities including topical, systemic, periocular and intraocular steroids; topical non-steroidal anti-inflammatory drugs (NSAIDs) and systemic carbonic anhydrase inhibitors have been used with different success rates to treat pseudophakic CME.<sup>3-5</sup>

The exact etiology of pseudophakic CME remains unknown, but intraocular inflammation appears to play a key role in its development. Vascular endothelial growth factor (VEGF) has been shown to be associated with breakdown of the blood retinal barrier and increased vascular permeability thereby contributing to

the development of macular edema.<sup>7,8</sup>

Bevacizumab (Avastin, Genentech Inc., South San Francisco, CA, USA) is a monoclonal antibody that inhibits all VEGF isoforms. It has not been approved for treatment of ocular diseases, however its "off-label" intraocular injection has been widely used for treatment of different ocular diseases associated with neovascularization and increased vascular permeability.<sup>9-14</sup> In this article, we review studies published on the use of intravitreal bevacizumab (IVB) injection for treatment of pseudophakic CME.

## METHODS

A literature search of all articles available on Medline and Scopus databases was performed using the keywords "cystoid macular edema", "anti-vascular endothelial growth factor", "bevacizumab", and "Avastin". Original and review articles, letters, and case reports, from January 2005 to October 2011 were reviewed. Given the expectation that the number of relevant studies would be quite small, all publications reporting the use of IVB for treatment of post cataract surgery CME were included and no restriction was placed on the level of evidence for inclusion.

## RESULTS

Eleven publications have reported the outcomes of IVB injection for the treatment of pseudophakic CME (Table 1).<sup>15-25</sup> These include one prospective<sup>15</sup> and four retrospective studies,<sup>16-19</sup> as well as four case reports,<sup>20-23</sup> one letter to editor<sup>24</sup> and one review article<sup>25</sup>.

The aim of the only prospective study was to evaluate the addition of topical NSAIDs to intravitreal injections for treatment of chronic CME. All patients were treated with combined intravitreal triamcinolone (IVTA) and IVB initially, and additional IVB in the fourth week. Patients were then randomized to receive a topical NSAID (diclofenac 0.1%, ketorolac 0.4%, nepafenac 0.1%, or bromfenac 0.09%) or placebo for 16 weeks. Improvement in visual acuity and retinal thickness was reported in both placebo

and NSAID groups, but the use of IVTA along with IVB confounds the results and makes the effect of IVB on CME questionable.

Two of the retrospective case series reported IVB injection for chronic and refractory CME after several weeks of medical therapy.<sup>16,19</sup> In another retrospective study, although pre-injection medical therapy was not an inclusion criteria, most patients (14/16) had a history of unsuccessful medical treatment.<sup>17</sup> In the other retrospective study, IVB was primarily injected in eyes with CME without history of previous medications.<sup>18</sup> Three of these studies reported significant improvement in visual acuity and reduction in retinal thickness in all or the majority of eyes after single or repeated IVB injections.<sup>16,18,19</sup> In contrast, one study reported improvement of visual acuity in only one eye (1/16) despite significant reduction in retinal thickness in 81% of eyes, and stable or decreased vision in the other 15 eyes.<sup>17</sup> The authors speculated that lack of visual improvement might be due to inadequate decrease in central retinal thickness as most patients still had considerable macular edema after IVB injection. Alternatively, they reported that in some patients, long standing CME might have been responsible for the low potential of visual recovery.

In one case report, IVB injection was shown to cause an increase in retinal thickness despite stability of vision.<sup>23</sup> CME improved significantly or resolved completely in other case reports.<sup>20-22</sup>

## Quality of the evidence

All of the studies reported in this article except one, were case reports and retrospective case series which are classified as very low and low quality studies due to their limitations.<sup>26</sup> The only prospective study also had low quality regarding the subject of our review.

## CONCLUSIONS

The treatment of postoperative CME remains controversial, mainly because the mechanism of increased endothelial permeability is not definitely known. Several factors have been implicated in the development of pseudophakic

**Table 1.** Clinical studies reporting IVB injection for treatment of pseudophakic CME

Authors	Design	Number of eyes	Intervention	Inclusion criteria	Interval between Dx and IVB	Follow-up	Visual outcome	Anatomical outcome
Warren et al <sup>15</sup>	Prospective	39 (8 in IVB+ placebo, 31 in IVB+ NSAID)	IVB+ IVTA at entry, repeat IVB at 4 weeks	Chronic CME	Mean 9.4 months (6-12)	16 weeks	Improved in all groups, more in nepafenac	Significant improvement in OCT, more in nepafenac
Arevalo et al <sup>16</sup>	Retrospective	36	IVB mean 2.7 (1-6) times	At least 3 months of medical therapy	Mean 10.6 months (3-60)	12 months	Improved $\geq 2$ lines in 72.2%	Significant improvement in OCT
Spitzer et al <sup>17</sup>	Retrospective	16	IVB (1-4)	Pre IVB medications in 14 eyes	Median 14 weeks (3-84)	14-82 weeks	Improved $\geq 2$ lines in 1, stable in 12, worsening in 2 eyes	Significant improvement in OCT, more than 10% decrease in 9 eyes
Arevalo et al <sup>18</sup>	Retrospective	28	IVB, 8 (28.6%) eyes 2nd injection, 4 (14.3%) eyes 3rd injection	Primary injection	Mean 13 months (1-60)	32 weeks (24 -52)	Improved $\geq 2$ lines in 71.4%, no vision loss	Significant improvement in OCT
Barone et al <sup>19</sup>	Retrospective	10	IVB	Refractory CME	17.5 weeks (11-24)	6 months	Improved in all eyes	Significant improvement in OCT
Díaz-Llopis et al <sup>20</sup>	Case Report	1	IVB	Chronic CME with 2 IVTA injections	19 months	2 months	Improved	Significant improvement in OCT
Mason et al <sup>21</sup>	Case Report	2	IVB	Refractory CME			Improved	Complete resolution of CME
Barone et al <sup>22</sup>	Case Report	1	IVB	Refractory CME		3 months	Improved	Complete resolution of CME
Sabet-peyman et al <sup>23</sup>	Case Report	1	IVB	Refractory CME, recurred after successful treatment with IVTA		1 month	No change	Worsening of CME

CME, cystoid macular edema; Dx, diagnosis; IVB, intravitreal bevacizumab; IVTA, intravitreal triamcinolone acetonide  
 OCT, optical coherence tomography; NSAID, non-steroidal anti-inflammatory drug

CME, including but not limited to inflammation with release of mediators such as prostaglandins and leukotrienes, vascular instability, vitreomacular traction, ocular hypotony, and ultraviolet light damage.<sup>4,25</sup> Considering the key role of inflammation in the development of pseudophakic CME, the focus of conventional treatments, including steroids and NSAIDs, is to eliminate the inflammatory process. In the presence of vitreomacular traction unresponsive to medical therapy, surgical modalities including laser vitreolysis and vitrectomy may

be considered as alternatives.

In a recent article, Shelsta and Jampol reported the 2010 update for treatment of pseudophakic CME.<sup>25</sup> They considered pseudophakic CME affecting patient’s vision 2 to 3 months post-operatively as an indication for treatment. They recommended a combination of a topical NSAID (less-expensive variety) and a topical corticosteroid at the beginning, and considered a more expensive topical NSAID if no improvement in vision was noted after 4 to 6 weeks. For refractory cases, they recommended

intravitreal injection of a corticosteroid.

Since pseudophakic CME is a common and usually self-limited condition, and considering the lack of well-designed randomized clinical trials evaluating the effect of various treatment modalities, we agree with Shelsta and Jampol who suggested a stepwise algorithm for treatment of pseudophakic CME. Although a theoretical role may be considered for VEGF inhibitors, there is no high quality evidence to recommend anti-VEGF agents as routine treatment for pseudophakic CME. However, IVB injection may be considered for patients with refractory CME unresponsive to intravitreal steroids. In the future, larger controlled studies are required to elucidate the role of intravitreal anti-VEGF agents for treatment of pseudophakic CME.

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