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Potential Beneficial Effects of Intravitreal Bevacizumab as an Adjuvant in Bacterial Endophthalmitis

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Abstract. Bacterial endophthalmitis is one of the most serious complications of ocular surgery and penetrating globe injury. Its management still remains a clinical challenge despite to attendant of intravitreal powerful wide spectral antibiotic use and vitrectomy. Irreversibly damage of the neurosensory retina and pigment epithelium is the major cause of the poor visual prognosis in bacterial endophthalmitis. The inflammation process which is related to increased vascular permeability and breakdown of the blood retinal barrier is the main pathological event during bacterial endophthalmitis. It is obvious that treatments to inhibit the inflammatory processes which can damage the eye in endophthalmitis are necessary. Despite the controversy, dexamethasone is frequently used as an adjunct to antibiotics for the treatment of endophthalmitis. The role of VEGF in inflammation has complex interactions. Increased permeability and enhanced leukocyte rolling and adhesion provided by VEGF play important roles in inflammation and other pathological situations. As a consequence of these data, we hypothesized that VEGF inhibitors may repair blood-retina barrier and diminish enhanced vascular permeability and decrease neutrophil recruitment into vitreous leading to ocular tissue destruction in bacterial endophthalmitis. Depletion of neutrophil recruitment into the vitreous may prolong bacterial clearance and may increase bacterial proliferation. However, restoring vascular permeability may also prevent nutrient and protein leakage into the vitreous and cause low bacterial proliferation rate. Simultaneous uses of intravitreal antibiotics undertake main bacterial clearance. Future studies defining the therapeutic effect of VEGF inhibitors combined with antibiotics might support our new hypothesis suggesting VEGF inhibitors as an alternative adjuvant treatment option in bacterial endophthalmitis.

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Abbreviations used: EVS, endophthalmitis vitrectomy study; VEGF, vascular endothelial growth factor

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1. Introduction

Bacterial endophthalmitis is one of the most serious complications of ocular surgery and penetrating globe injury. Its management still remains a clinical challenge despite to attendant of intravitreal powerful wide spectral antibiotic use and vitrectomy. Decreased vision and permanent loss of vision are common complications of endophthalmitis. Cases treated in the Endophthalmitis Vitrectomy Study (EVS), 84% of all patients achieved at least 20/100 visual acuity, while 50% of these patients resulted in 20/40 visual acuity despite to successful/adequate treatment [1].

Irreversibly damage of the neurosensory retina and pigment epithelium is the major cause of the poor visual prognosis in bacterial endophthalmitis. Prognosis and severity of the endophthalmitis depend on multiple factors such as type and virulence of causative microorganism, different ocular conditions, duration of the infection, delayed or missed diagnosis, attendant systemic diseases etc. It is believed that cause of the ocular tissue damage from endophthalmitis is primarily a result of effects from the severe inflammatory response against infection in addition to direct effects caused by bacterial organism [2]. Neutrophils are responsible for the innate host immunity and eliminate infecting organism by phagocytosis. During the elimination process a number of toxic oxygen radicals and lysozymal enzymes release into the vitreous and may cause further tissue damage [3]. However, it's suggested that longstanding culture negative ocular inflammation and subsequent tissue damage in infectious endophthalmitis mainly due to the host immune response [4]. Control of the host inflammatory response and elimination of infecting organism have been also recommended [5]. Thus, the inflammation process which is related to increased vascular permeability and breakdown of the blood retinal barrier is the main pathological event during bacterial endophthalmitis. It may also convert vitreous as a culture medium by promoting leakage of nutrients, fluid and protein from blood vessels into the vitreous and increase bacterial proliferation.

It is obvious that treatments to inhibit the inflammatory processes which can damage the eye in endophthalmitis are necessary. Moreover, depletion of neutrophils early in the inflammatory response delayed the onset of severe ocular inflammation but also prevented adequate bacterial clearance. These results confirm the important role of neutrophils in ocular host defense during the early stages of experimental endophthalmitis [6]

Systemic, subconjunctival, and topical steroids are commonly employed to suppress host inflammatory response. There are contradictory data which suggest that direct intravitreal steroid administration (dexamethasone 400 µg) for treatment of endophthalmitis. Experimental and clinical studies have reported that concomitant administration of dexamethasone with antibiotics were harmful [7], beneficial [8, 9] or had no effect [10, 11]. Despite the controversy, dexamethasone is frequently used as an adjunct to antibiotics for the treatment of endophthalmitis.

2. VEGF and Its Inhibitors

Vascular endothelial growth factor (VEGF) initially described as "vascular permeability factor" in 1983, the molecule later was described independently as VEGF and subsequently discovered to be the same [12, 13]. The role of VEGF in inflammation has complex interactions. It has been reported that VEGF and basic fibroblast growth factor differentially enhance monocyte and neutrophil recruitment into inflamed tissue [14]. Increased permeability and enhanced leukocyte rolling and adhesion provided by VEGF play important roles in inflammation and other pathological situations [15].

Bevacizumab is a full-length recombinant humanized antibody, active against all isoforms of VEGF, and approved for use in colorectal cancer [16]. Since the neovascularization and increased vascular permeability characteristics of such retinal diseases, Intravitreal injection of VEGF inhibitors has become increasingly common in retinal diseases such as macular edema secondary to central retinal venous occlusion or diabetic retinopathy and neovascular age related macular degeneration [17-19].

3. Hypothesis

As a consequence of these data, we hypothesized that VEGF inhibitors may repair blood-retina barrier and diminish enhanced vascular permeability and decrease neutrophil recruitment into vitreous leading to ocular tissue destruction in bacterial endophthalmitis. Reduced vascular permeability and diminished neutrophil recruitment by VEGF inhibitors may prevent neutrophil influx into the vitreous and suppress indirectly host immunity, which is expected from an adjuvant dexamethasone use. Depletion of neutrophil recruitment into the vitreous may prolong bacterial clearance and may increase bacterial proliferation. However, restoring vascular permeability may also prevent nutrient and protein leakage into the vitreous and cause low bacterial proliferation rate. Simultaneous uses of intravitreal antibiotics undertake main bacterial clearance. Thus, course of endophthalmitis may be forwarded in a long time and in a less vigorous form.

The estimated incidences of endophthalmitis following intravitreal injection of bevacizumab and triamsinolon have been reported as 0.014%, and, between 0.099% and 0.87% per injection, respectively [20-22]. Despite the other influencing factors such as increased tendency of infections with steroids, the lower incidence of endophthalmitis following intravitreal injection of bevacizumab may be explained by our hypothesis. Future studies defining the therapeutic effect of VEGF inhibitors combined with antibiotics might support our new hypothesis suggesting VEGF inhibitors as an alternative adjuvant treatment option in bacterial endophthalmitis.

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