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Efficacy and safety of anti-vascular endothelial growth factor agents on corneal neovascularization: a meta-analysis

Shih-Chung Lai, El-Wui Loh, Du-I Chiou, Chien-Tai Hong

Abstract

BACKGROUND

Corneal neovascularization (CoNV) is the second major cause of blindness. Vascular endothelial growth factor (VEGF) inhibitors, *e.g.*, bevacizumab, have been used to prevent CoNV.

AIM

We conducted an updated systematic review and meta-analysis of clinical trials to examine the efficacy and safety of anti-VEGF in CoNV.

METHODS

A literature search was conducted using three electronic databases. Mean difference (MD), standard mean difference (SMD), and relative risk (RR) are used to estimate the effect size.

RESULTS

Nine randomized controlled and three non-randomized trials were obtained. The pooled results demonstrated a significant reduction of CoNV area/Length (SMD = -1.17, 95%CI: -1.58 to -0.75), best corrected visual acuity (BCVA) (MD = -0.54, 95%CI: -0.91 to -0.17), and graft rejection (RR = 0.44, 95%CI: 0.24 to 0.8) and failure (RR = 0.39,

95%CI: 0.19 to 0.78) rates in the anti-VEGF group than the placebo group. A non-significant reduction of the epithelial defect was also observed in the bevacizumab group compared with the placebo (RR = 0.56, 95%CI: 0.30 to 1.06). Compared with a placebo, the unsynthesizable trials also support that bevacizumab improves visual acuity, CoNV, graft rejection, and failure rates. Trials reporting other comparisons revealed the superiority of combined remedy with bevacizumab compared to other treatments in reducing CoNV.

CONCLUSION

Anti-VEGF agents, mainly bevacizumab, are an effective and safe treatment for CoNV of all causes and prevent corneal graft rejection and failure in corneal transplantation.

INTRODUCTION

Corneal neovascularization (CoNV) is a condition of pathological vascular ingrowth into the cornea from the limbus, causing the avascular structure to become non-transparent and further markedly threaten the visual acuity. CoNV may be induced by infection, chemical injury, burn, trauma, autoimmune problems, post-corneal surgery, contact lens wearing, and other factors leading to inflammation. Skobe *et al* indicated that CoNV is the second cause of blindness worldwide [1]. Lee *et al* reported that CoNV develops in an estimated 1.4 million patients in the United States annually, and 12% of these cases are associated with decreased visual acuity [2]. Lasagni Vitar *et al* conducted a 14-year retrospective study reviewing 13,493 charts in Italy and found that 10.4% of the patients had CoNV, and severe CoNV (three or four of the quadrants) was a significant predictor of low visual acuity [3]. CoNV also reduces the immune privilege of the cornea, which increases the rejection rate of corneal transplantation [4, 5].

Various treatment approaches, including anti-inflammatory drugs (e.g., steroids and immunomodulators), laser ablation, photodynamic therapy (PDT), diathermy, and ocular surface restoration, have been used in CoNV management. These approaches are

not without problems. Topical steroid use is associated with multiple adverse effects, such as glaucoma and cataracts. A few studies show that PDT is effective and safe for CoNV treatment [6-8], but the technique is time-consuming and relatively expensive. Another effective drug for CoNV is the vascular endothelial growth factor (VEGF) inhibitor. VEGF inhibitors prevent CoNV by blocking the VEGF pathways that promote the survival, proliferation, and migration of vascular endothelial cells that causes neovascularization [9]. Bevacizumab (Avastin) is the most used anti-VEGF drug - a recombinant humanized monoclonal immunoglobulin that binds to VEGF-A, one of the VEGF isoforms in humans. A systematic review and meta-analysis in 2013 that included seven human and 18 experimental animal studies concluded that bevacizumab significantly reduced CoNV [10]. Several randomized controlled trials (RCTs) and non-randomized trials (NRTs) examining the efficacy of anti-VEGF in CoNV have been published in the past few years. In this study, we conducted an updated systematic review and meta-analysis of clinical trials to examine the efficacy and safety of anti-VEGF in CoNV.

MATERIALS AND METHODS

Corneal neovascularization (CoNV) is a condition of pathological vascular ingrowth into the cornea from the limbus, causing the avascular structure to become non-transparent and further markedly threaten the visual acuity. CoNV may be induced by infection, chemical injury, burn, trauma, autoimmune problems, post-corneal surgery, contact lens wearing, and other factors leading to inflammation. Skobe *et al* indicated that CoNV is the second cause of blindness worldwide [1]. Lee *et al* reported that CoNV develops in an estimated 1.4 million patients in the United States annually, and 12% of these cases are associated with decreased visual acuity [2]. Lasagni Vitar *et al* conducted a 14-year retrospective study reviewing 13,493 charts in Italy and found that 10.4% of the patients had CoNV, and severe CoNV (three or four of the quadrants) was a significant predictor of low visual acuity [3]. CoNV also reduces the immune privilege of the cornea, which increases the rejection rate of corneal transplantation [4, 5].

Various treatment approaches, including anti-inflammatory drugs (e.g., steroids and immunomodulators), laser ablation, photodynamic therapy (PDT), diathermy, and ocular surface restoration, have been used in CoNV management. These approaches are not without problems. Topical steroid use is associated with multiple adverse effects, such as glaucoma and cataracts. A few studies show that PDT is effective and safe for CoNV treatment [6-8], but the technique is time-consuming and relatively expensive. Another effective drug for CoNV is the vascular endothelial growth factor (VEGF) inhibitor. VEGF inhibitors prevent CoNV by blocking the VEGF pathways that promote the survival, proliferation, and migration of vascular endothelial cells that causes neovascularization [9]. Bevacizumab (Avastin) is the most used anti-VEGF drug - a recombinant humanized monoclonal immunoglobulin that binds to VEGF-A, one of the VEGF isoforms in humans. A systematic review and meta-analysis in 2013 that included seven human and 18 experimental animal studies concluded that bevacizumab significantly reduced CoNV [10]. Several randomized controlled trials (RCTs) and non-randomized trials (NRTs) examining the efficacy of anti-VEGF in CoNV have been published in the past few years. In this study, we conducted an updated systematic review and meta-analysis of clinical trials to examine the efficacy and safety of anti-VEGF in CoNV.

RESULTS

Search Results

Figure 1 illustrates the flowchart of screening and selection of trials. The initial search identified 746 records. After removing 220 duplicates, 526 records were screened by titles and abstracts. A total of 254 irrelevant records, 116 cell or animal studies, 51 review or commentary articles, six letters, four conference abstracts, five clinical trial protocols, and one systematic review and meta-analysis were excluded. With careful examination of the contents, we removed 73 case reports/series or single-arm studies, three studies using duplicate samples, and one retrospective case-control study. Finally, we included nine RCTs [15-23] and three NRTs [24-26].

Table 1 summarizes the characteristics of the included RCTs and NRTs. The sample size of these studies ranged from 7 to 92 patients. Most trials reported the age and gender information of the patients. The follow-up period ranged from one month to three years. The inclusion criteria of these trials varied. Four RCTs recruited patients with CoNV of different pathologies, four RCTs and two NRTs recruited patients undergoing high-risk transplantations, and one RCT and one NRT recruited patients undergoing recurrent pterygium surgery. The dosage and the frequency of the anti-VEGF drugs also differed.

Risk of Bias

The upper part of Table 2 summarizes the assessment results of risk of bias for RCTs, and the lower part summarizes the assessment results for NRTs. For RCTs, two trials were of high risk in the bias arising from the randomization process (D1) because they did not conceal the allocation sequence [15, 20], five trials were of some concerns because they had imbalance baselines or did not report the allocation sequences [17-19, 21, 23], and the remaining two trials were of low risk. In the bias due to deviations from intended interventions (D2), three trials were of some concerns because two of them were open labeled without information on deviation [15, 17], and one did not report information on blinding or deviation [21]. The remaining six trials were of low risk. In the bias due to missing outcome data (D3), one trial was of high risk due to missing data without explanations [15], two trials were of some concerns because no information of missing data was described [17, 20], and the remaining six trials were of low risk. In the bias in the measurement of the outcome (D4), all trials were of low risk. In the bias in the selection of the reported result (D5), one trial was of high risk because the results were reported incompletely [15], and the remaining eight trials were of low risk. For the overall risk, two RCTs were of low risk [16, 22], four RCTs were of some concerns [18, 19, 21, 23], and three RCTs had a high risk [15, 17, 20].

For NRTs, two studies were of moderate risk in the bias due to confounding (D1) due to the lack of baseline information or appropriate analysis to control the

confounding [25, 26], two trials were of moderate risk in the bias due to missing data (D5) because they did not report the missing data [24, 26], and two trials were of serious risk in the bias in the selection of the reported result (D7) because statistical analyses were not conducted in these trials [25, 26]. All three NRTs were of low risk in the bias in the selection of participants into the study (D2), bias in the classification of interventions (D3), bias due to deviations from intended interventions (D4), and bias in the measurement of outcomes D6. For the overall risk, one NRT had a moderate risk [24], whereas the other two NRTs had a serious risk [25, 26].

General Issues

Because a large proportion of included trials/studies of our study could not be synthesized, we summarized all findings in Table 3 for overview and pooled those which were synthesizable. Among the 12 trials included, one compared different types of anti-VEGF (bevacizumab to ranibizumab)[19], one compared different doses of bevacizumab[23], and one compared different frequencies of ranibizumab [25]. We described the review results in the last subsection for ease of understanding.

Corneal Neovascularization

Five trials reported the comparison of bevacizumab on CoNV with a placebo [15,16,20-22]. Three trials reported pre-treatment, reduced, and/or post-treatment CoNV area/Length at 3 mo [22], 1 year [16], and 3 years [20], respectively, were used in the meta-analysis (Figure 2). The pooled results demonstrated no significant difference in post-treatment CoNV area between the bevacizumab group and the placebo group (SMD = -1.77, 95%CI: -4.65 to 1.11) with high heterogeneity across trials (p = 0.02, I^2 = 83%), but a significant reduction of CoNV area/Length in the bevacizumab group than the placebo group (SMD = -1.17, 95%CI: -1.58 to -0.75) without heterogeneity across trials (p = 0.32, I^2 = 0%). Among the two trials that cannot be pooled, Ozgurhan *et al* compared the number of patients having recurrent CoNV in the bevacizumab group with the placebo group at 1 mo, 2 mo, 3 mo, and 6 mo, and concluded that bevacizumab significantly

reduced the number of patients with recurrent CoNV [21]; Bhatti *et al* reported CoNV area in 4 wk and 24 wk after receiving corneal transplantation, and a significant reduction of CoNV area was reported without providing mean and standard deviation [15].

Best Corrected Visual acuity

Five trials compared the effect of bevacizumab on BCVA with a placebo [15, 16, 20, 22, 24]. Two of them reported that the mean pre-treatment and post-treatment BCVA data at the follow-up endpoint were used in the meta-analysis [22, 24]. Figure 3 demonstrates the pooled effect of bevacizumab on BCVA. The results revealed a significantly better BCVA outcome in the bevacizumab group (MD = -0.54, 95%CI: -0.91 to -0.17) than in the placebo group without heterogeneity across trials (p = 0.4, I^2 = 0%). The results of the remaining three trials that cannot be pooled are mentioned below. Among them, Li *et al* reported partial VA improvement without providing statistical details [20]. Bhatti *et al* [15] and Dohlman *et al*[16] reported the comparisons in four VA ranges. Bhatti *et al* reported a significantly better VA in the bevacizumab group without providing the pre-treatment VA data [15], while Dohlman *et al* reported pre-treatment VA and post-treatment VA range at 4, 8, 16, 26, and 52 wk and found no significant VA difference between the two groups at any time point [16].

Graft Rejection and Failure Rates

Five trials compared the effect of anti-VEGF drugs with placebo on graft rejection and/or overall survival rates after corneal transplantation [16, 17, 20, 24, 26]. Li *et al* indicated graft rejection decreased in groups using bevacizumab, but the rejection and failure rate details were not reported [20]. The remaining four trials with mean follow-up duration ranging from 14.3±2.2 to 26.1±5.7 mo were used in the meta-analysis (Figure 4) [16, 17, 24, 26]. The result revealed significantly lower graft rejection (RR = 0.44, 95%CI: 0.24 to 0.8) and failure (RR = 0.39, 95%CI: 0.19 to 0.78) rates in the anti-VEGF group compared with

placebo, with low heterogeneity across trials (p = 0.36, I^2 = 2%; p = 0.17, I^2 = 46% respectively).

Adverse Events

Two of the 12 trials included in this study did not report adverse event information [15, 20]. Dohlman *et al* reported that one patient developed atrial fibrillation in the bevacizumab group. However, it was not considered related to the treatment [16]. For local adverse events, Kim *et al* reported persistent epithelial defects with corneal melting after the bevacizumab injection in two patients with limbal stem cell deficiency [19]. The other three trials also reported corneal epithelial defects. However, most patients healed after treatments using local antibiotics, artificial tears, and bandage contact lens [16, 22, 24]. Other minor local adverse events such as foreign body sensation, pain, subconjunctival hemorrhage, photophobia, and tearing were noted [16, 17, 21-24]. Because bevacizumab may harm epithelial healing, we pooled the three trials that compared bevacizumab with placebo with epithelial defect events reported for meta-analysis [16, 22, 24]. Figure 5 demonstrates the pooled effect of bevacizumab on the risk of developing epithelial defects. The results revealed a non-significant reduction of the risk of developing epithelial defect in the bevacizumab group compared with placebo (RR = 0.56, 95%CI: 0.30 to 1.06) and without heterogeneity across trials (p = 0.50, I^2 = 0%).

Others

This subsection describes the comparisons of different types of anti-VEGF agents, different dosages of bevacizumab, and different frequencies of ranibizumab on CoNV. Li *et al* [20] and Hamdan *et al* [18] compared the efficacy bevacizumab with other types of treatment. Li *et al* compared bevacizumab with triamcinolone acetonide and combined therapy of bevacizumab and triamcinolone acetonide and found that both bevacizumab and combined therapy groups significantly reduced CoNV compared with the triamcinolone acetonide group [20]. Hamdan *et al* compared bevacizumab with PDT and

combined therapy of bevacizumab and PDT with a follow-up period of six months; the combined therapy showed a non-significant tendency toward greater efficacy than single monotherapies in reducing CoNV [18]. Kim *et al* compared the efficacy of bevacizumab with ranibizumab in a 1-month follow-up period. They found that the average decrease of CoNV area was significantly greater in the bevacizumab group than in the ranibizumab group, with a mean change of VA not showing a significant improvement in either group [19]. You *et al* compared the efficacy of bevacizumab at different dosages (1.25mg/0.05 mL, 2.5mg/0.1 mL, and 5.0mg/0.2 mL, subconjunctival route) in a 3-month follow-up period. They found that 2.5mg and 5mg of bevacizumab reduced the CoNV area significantly, but no VA improvement differences between groups [23]. Hurmeric *et al* compared the effect of ranibizumab in different frequencies (once or every two weeks for three times) and revealed no prominent role of recurrent injections over a single injection in reducing CoNV [25].

DISCUSSION

We found that anti-VEGF agents significantly reduced CoNV, BCVA, and graft rejection/failure rate compared with placebo. There was a non-significant trend toward reduction of the risk of developing corneal epithelial defects in the bevacizumab group compared with placebo. Also, combined remedies with bevacizumab have better efficacy in reducing CoNV compared with single other treatments. Per the previous systematic review and meta-analysis by Papathanassiou *et al* [10], we demonstrated that anti-VEGF agents significantly reduce CoNV in corneal transplantation, recurrent pterygium, and other pathologies. While Papathanassiou *et al* [10] did not find evidence supporting the efficacy of bevacizumab in improving VA, we demonstrated some evidence supporting the efficacy of bevacizumab in improving VA.

Among the included trials, one RCT revealed that bevacizumab is more effective than steroids in reducing CoNV [20]. Also, Kim *et al* found that the average reduction of CoNV area was significantly greater in the bevacizumab group than in the ranibizumab group [19]. Ranibizumab is a lower molecular weight anti-VEGF agent compared with

bevacizumab, and it is supposed to have a better penetration capacity than bevacizumab. Also, ranibizumab was reported to be more potent than bevacizumab and might provide better VEGF inhibition compared with bevacizumab [27]. However, it did not show better efficacy in reducing CoNV, according to Kim *et al* [19]. This might be caused by underdosing of ranibizumab. An ideal dose of ranibizumab needs further studies for clarification.

The effect of anti-VEGF drugs on VA appears to be affected by pre-treatment disease status. We noticed that those trials with worse pre-treatment VA tended to have a relatively noticeable VA change, and those with relatively better pre-treatment VA tended to have an unchanged post-treatment VA. Nevertheless, though not statistically significant, anti-VEGF drugs demonstrated a tendency to improve VA in patients with CoNV. For high-risk corneal transplantation, our study showed that anti-VEGF agents significantly decrease the risk of graft rejection and failure, possibly through the reduction of inflammatory responses, which is crucial to graft failure [28, 29]. Also, the reduction of NV of the host may decrease the exposure of graft antigens to the immune system and further reduce the rejection risk. Chong *et al* outlined the comprehensive immunologic mechanisms involved in corneal transplant rejection and indicated that both the afferent (allosensitization) and efferent (rejection) arms of the alloimmune response are enhanced in the presence of NV [4]. One previous meta-analysis also concluded that graft failure and rejection risk elevate along with the increase of corneal quadrants affected by neovascularization before the formation of keratoplasty [30].

Several animal studies indicated that bevacizumab delayed epithelial healing [31-33]. One included trial of our study reported two cases with persistent epithelial defects and corneal melting after the bevacizumab injection [19]. The authors suggested that bevacizumab should be carefully used, especially in patients with limbal stem cell deficiency. A case report described a patient with corneal melting after topical bevacizumab use for penetrating keratoplasty [34]; another case report described a patient with corneal thinning after intrastromal injection of bevacizumab for idiopathic lipid keratopathy [35]. However, our study showed no significant difference between

bevacizumab and placebo groups in the risk of developing epithelial defects. Indeed, more patients reported having epithelial defects in the placebo group than in the bevacizumab group. Accordingly, bevacizumab is generally safe for CoNV treatment.

Various routes, dosages, and frequencies of anti-VEGF agents are used for CoNV treatment. Previous experimental studies suggested that, although topically applied bevacizumab has limited capacity to penetrate the intact corneal epithelium, bevacizumab can penetrate the neovascularized cornea after topical application [36], and both topical and subconjunctival routes of administration could effectively decrease CoNV [37, 38]. The included trials of our study used both administration routes mentioned above, and they appeared to show similar efficacy. Our study could not reveal a solid conclusion for this aspect due to the limited data available. Further trials are still needed to seek the ideal administration of anti-VEGF agents in CoNV. Lastly, one of the limitations of the present study was the failure of providing evidence about the cost-effectiveness of different formulation of anti-VEGF agents, since no study included conducting this analysis.

While most of the meta-analyses showed no evidence of heterogeneity, two analyses demonstrated low and high levels of heterogeneity, which might arise from the clinical variety of the sample. First, different diagnostic criteria were used in the included trials. Second, the drug administration route, dosage, and frequency were inconsistent across trials. Third, the time points of outcome measurement differed across trials. This study consists of two main limitations. First, we included a limited number of RCTs, and the sample size per treatment group was small. Thus, the statistical power is weak. Second, several trials reported fragmented outcome information and thus increased the risk of bias.

CONCLUSION

The treatment for CoNV is an issue of debate in efficacy, safety, and cost. Bevacizumab is a relatively cheap anti-VEGF agent. In this study, we found evidence demonstrating that anti-VEGF agents, mainly bevacizumab, are an effective and safe treatment for

CoNV. Although the effect of improving VA remains ambiguous, anti-VEGF agents reduce CoNV of all causes and prevent the corneal graft from rejection and failure in corneal transplantation patients. However, the most appropriate dosage and route of administration remain uncertain. Also, the number of human trials or studies for anti-VEGF drugs other than bevacizumab is limited. Additional trials and studies with larger sample sizes are needed to clarify these issues.

ARTICLE HIGHLIGHTS

Research background

Corneal neovascularization (CoNV) is a condition of pathological vascular ingrowth into the cornea from the limbus, causing the avascular structure to become non-transparent and further markedly threaten the visual acuity. Various treatment approaches, including anti-inflammatory drugs (e.g., steroids and immunomodulators), laser ablation, photodynamic therapy (PDT), diathermy, and ocular surface restoration, have been used in CoNV management. These approaches are not without problems.

Research motivation

Several randomized controlled trials (RCTs) and non-randomized trials (NRTs) examining the efficacy of anti-VEGF in CoNV have been published in the past few years.

Research objectives

We conducted an updated systematic review and meta-analysis of clinical trials to examine the efficacy and safety of anti-VEGF in CoNV.

Research methods

Relevant studies published before October 2022 were identified by systematic search using PubMed, Embase, and Cochrane Library databases.

Research results

In this study, we found evidence demonstrating that anti-VEGF agents, mainly bevacizumab, are an effective and safe treatment for CoNV.

Research conclusions

Anti-VEGF agents significantly reduced CoNV, BCVA, and graft rejection/failure rate compared with placebo. There was a non-significant trend toward reduction of the risk of developing corneal epithelial defects in the bevacizumab group compared with placebo. Also, combined remedies with bevacizumab have better efficacy in reducing CoNV compared with single other treatments.

Research perspectives

Anti-VEGF agents reduce CoNV of all causes and prevent the corneal graft from rejection and failure in corneal transplantation patients. However, the most appropriate dosage and route of administration remain uncertain. Also, the number of human trials or studies for anti-VEGF drugs other than bevacizumab is limited. Additional trials and studies with larger sample sizes are needed to clarify these issues.

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