Effect of Intravitreal Anti-Vascular Growth Factor Agents With or Without Macular Photocoagulation on Diabetic Macular Edema: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Diabetes is a common cause of new sight loss in populations world-wide, and diabetic macular edema (DME) is a major cause of visual deficits in the diabetic populations of developed countries. We have performed a meta-analysis to evaluate whether combined treatment with anti-vascular endothelial growth factor (VEGF) injections and macular photocoagulation (MPC) is more efficacious than primary monotherapy with anti-VEGF injections in patients with DME.

Methods: We systematically searched the PubMed and Web of Science databases for studies providing sufficient information for a comparison of pre- and post-treatment of central macular thickness (CMT) and best-corrected visual acuity (BCVA) between two groups of patients with DME given interventional therapies (monotherapy with an anti-VEGF agent vs. combination therapy with an anti-VEGF agent and MPC) before January 2019. A meta-analysis was performed to summarize the results of the studies included in the systematic review.

Results: The results of our meta-analysis indicated that post-treatment CMT was significantly lower at 3 months in DME patients receiving combination therapy with bevacizumab, a humanized anti-VEGF antibody, and MPC than in those receiving monotherapy with bevacizumab. The results also showed that post-treatment CMT was lower in DME patients given ranibizumab, an anti-VEGF agent, in combination with MPC at 6, 9 and 12 months than in those treated with ranibizumab alone. However, no significant differences were found in post-treatment BCVA at 1, 3, 6, 9 and 12 months between DME patients receiving combination therapy with an anti-VEGF agent (bevacizumab or ranibizumab) and MPC and those receiving monotherapy with an anti-VEGF agent.

Conclusion: In conclusion, the results of our meta-analysis demonstrate a transiently synergistic effect of MPC on CMT when this treatment is combined with anti-VEGF agents, whereas no similar synergistic effect could be detected on the BCVA. A relatively longer follow-up was essential to be able to evaluate the long-term existence of this synergistic effect.
INTRODUCTION

Diabetic macular edema (DME) is a condition that results from fluid accumulation in the macula and cystoid edema of the macula, usually accompanied by exudate deposition. It can be attributed to diabetic retinopathy, which causes swelling in the macula [1]. With the steady increase in the prevalence of diabetes worldwide, DME is considered to be one of the main causes of visual deficits in the populations of developed countries, affecting 7% of diabetic patients [2, 3].

The traditional treatments of DME are intravitreal triamcinolone, macular photocoagulation (MPC) and pars plana vitrectomy, in combination with adequate control of the diabetes and hypertension [4]. More recently, anti-vascular endothelial growth factor (anti-VEGF) injections have become the standard of care for eyes with DME and vision impairment [5]. In the past decade, a number of studies have shown that anti-VEGF injections are effective in reducing central macular thickness (CMT) and improving best-corrected visual acuity (BCVA) [6, 7]. However, anti-VEGF agents are not able to treat macular hypoxia, which is the main cause of DME [6], and thus the effects of anti-VEGF agents are transient. In addition, the duration of action of anti-VEGF agents is limited, as exemplified by the short half-life of bevacizumab and ranibizumab, both anti-VEGF agents, in eyes of 9.8 days and 2.75 days, respectively, resulting in the recurrence of macular edema in eyes treated with anti-VEGF agents within a few weeks [8–11]. Laser photocoagulation has been shown to cause damage to some, but not all photoreceptors and to reduce the high oxygen consumption of the photoreceptors by a pathway different from that of anti-VEGF agents [12]. Consequently, the combination of MPC and anti-VEGF injections may be an effective therapy to prolong the effectiveness of anti-VEGF agents and contribute to a better result by reducing macular hypoxia. In addition, the effectiveness of MPC may be enhanced by MPC becoming easier due to a reduction of macular edema by anti-VEGF injections. A number of recent studies have indicated that treatment with anti-VEGF agents in combination with MPC is superior to therapy with an anti-VEGF agent alone in terms of reducing CMT and improving BCVA in patients with DME [9, 13]. However, other studies have reported that there was no significant difference in CMT reduction and BCVA improvement between DME patients given anti-VEGF agents in combination with MPC and those given anti-VEGF agents alone [14, 15].

We have therefore performed a meta-analysis to evaluate whether combination therapy with anti-VEGF agents and MPC is more efficacious than primary monotherapy with anti-VEGF injections in terms of DME treatment.

METHODS

The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Search Strategy, Inclusion Criteria, Exclusion Criteria and Data Collection

We performed a systematic search of the PubMed and Web of Science databases for articles written in English and published up to January 2019. The search terms used were: “bevacizumab” OR “avastin” OR “aflibercept” OR “ranibizumab” OR “conbercept” OR “anti-VEGF” OR “anti-vascular endothelial growth factor” AND “photocoagulation” AND “diabetic
macular edema”. This search strategy resulted in the identification of 354 articles once duplicate studies had been excluded.

The inclusion criteria were randomized controlled trials (RCTs) or high-quality comparative studies that provided sufficient data for a comparison of pre- and post-treatment CMT and BCVA between two groups of DME patients given interventional therapies (anti-VEGF agents alone vs. combination therapy of anti-VEGF agents and with MPC).

The exclusion criteria were: (1) articles which did not provide sufficient data on pre- and post-treatment CMT and BCVA; (2) reviews, meta-analyses and case studies.

Two reviewers independently extracted the following data: author, publication year, research type, location of the study, number of eyes and mean age of patient, information on treatment (dosage of anti-VEGF agents, mean time of anti-VEGF agents during follow-up, and type of MPC), duration of follow-up and treatment outcome.

Meta-Analysis

The weighted mean difference in CMT and BCVA with the 95% confidence interval was obtained using STATA version 12.0 software (StataCorp LP, College Station, TX, USA) to estimate the treatment effect. The $Q$ test and $I^2$ were applied to evaluate the heterogeneity between included studies. Random effects models were used when there was high heterogeneity ($p$ value for $Q$ test $\leq 0.05$), otherwise, fixed effects models were used. A sensitivity analysis was performed by removing one individual study each time to evaluate the stability of the meta-analysis. Additionally, subgroup analyses (for different anti-VEGF agents and different study designs) were conducted to explore the impact of heterogeneous types of anti-VEGF agents and research types on the heterogeneity of the meta-analysis. Sensitivity analyses were also conducted to evaluate the stability of the meta-analysis. Publication bias was evaluated using Begg’s test, Egger’s test and funnel plots.

RESULTS

Search Results

A flow chart showing the results of the initial research and subsequent progression in the selection process is given in Fig. 1. Table 1 shows the characteristics and results of the 12 studies ultimately included in the meta-analysis. All 12 studies (10 RCTs, 2 retrospective studies) compared post-treatment CMT and BCVA between two groups of DME patients given interventional therapies (monotherapy with an anti-VEGF agent vs. combination therapy with an anti-VEGF agent and MPC) and included 748 patients who received monotherapy with an anti-VEGF agent and 663 patients who were given combination therapy with an anti-VEGF agent and MPC. Of the 12 studies, five used bevacizumab as the anti-VEGF agent, six used ranibizumab, and one used conbercept.

Meta-Analysis Results

The meta-analysis indicated that post-treatment CMT at 3, 6 and 9 months was significantly lower in DME patients given combination therapy with an anti-VEGF agent and MPC than in DME patients receiving monotherapy with an anti-VEGF agent, but that no significant differences in CMT were detected between two groups at 1 and 12 months of follow-up (see Fig. 2). Subgroup analyses showed that DME patients given bevacizumab in combination with MPC showed significantly lower post-treatment CMT at 3 months than did those given bevacizumab alone, whereas no significant differences in post-treatment CMT were detected between the two groups at 6 and 12 months. However, DME patients given combination therapy with ranibizumab and MPC showed significantly lower post-treatment CMT at 3 months than did those receiving monotherapy with ranibizumab, whereas no significant differences in post-treatment CMT were detected between the two groups at 6 and 12 months. However, DME patients given combination therapy with ranibizumab and MPC showed significantly lower post-treatment CMT at 6, 9 and 12 months than did those receiving monotherapy with ranibizumab, whereas no significant differences in post-treatment CMT were detected between the two groups at 3 months (see Fig. 3). Subgroup analyses showed that the results were the same when only the ten RCTs were included in the
Our meta-analysis showed no significant differences in post-treatment BCVA at 1, 3, 6, 9 and 12 months between DME patients given combination therapy with an anti-VEGF agent and MPC and those given monotherapy with an anti-VEGF agent (see Fig. 5). The subgroup analyses did not detect any significant differences in terms of anti-VEGF agent administered (bevacizumab or ranibizumab; see Fig. 6). In addition, the meta-analysis including only the RCTs revealed no significant differences in post-treatment BCVA between the two patients groups at all follow-up points (see Fig. 7).

The sensitivity analysis showed no changes in the direction of effect when any one study was excluded for all meta-analyses at different follow-up points (see Electronic Supplementary Material [ESM] Fig. 1). Moreover, Begg’s test, Egger’s tests and funnel plots did not detect any significant risk of publication bias for all meta-analyses at different follow-up points (see ESM Table 1 and Fig. 2).

**DISCUSSION**

The results of our meta-analysis indicated that post-treatment CMT was significantly lower at 3 months of follow-up in DME patients given...
| First author/reference | Study design | Country | No. of eyes | Anti-VEGF group | Anti-VEGF + MPC group | Age (years)* | Dosage of IVB (mg) | Type of MPC | Length of follow-up (months) | Anti-VEGF agents |
|-----------------------|--------------|---------|-------------|-----------------|-----------------------|--------------|-------------------|-------------|-----------------------------|----------------|
| Das [13]              | RCT          | India   | 30          | 30              | 30                    | 54.63 (8.34) | 1.25             | Grid        | 3, 6                       | Bevacizumab     |
| Solaiman [9]          | RCT          | Egypt   | 21          | 22              | 56                    | 59           | 1.25             | Focal/grid  | 1, 3, 6                    | Bevacizumab     |
| Arevalo [14]          | RCT          | USA     | 141         | 157             | 59.4 (10.8)           | 62.2 (8.7)  | 1.25 or 2.5      | Grid        | 1, 3, 6, 12, 24            | Bevacizumab     |
| Lee [15]              | RCT          | Korea   | 38          | 90              | 61.2 (8.8)            | 59.8 (4.1)  | 2.5              | Grid        | 1                          | Bevacizumab     |
| Javanovic [18]        | RCT          | Serbia  | 31          | 53              | NA                    | NA           | 1.25             | Focal/grid  | 1                          | Bevacizumab     |
| Mitchell [20]         | RCT          | Australia | 118       | 116             | 62.9 (9.29)           | 64.0 (8.15) | 0.5              | Focal/grid  | 12                         | Ranibizumab     |
| Nguyen [24]           | RCT          | USA     | 42          | 42              | 62                    | 62           | 0.5              | Focal/grid  | 3                          | Ranibizumab     |
| Herold [25]           | Retrospective study | Germany | 13         | 11              | 67.4 (11.8)           | 65.8 (9.1)  | 0.5              | Focal/grid  | 6, 12, 18, 24, 30, 36       | Ranibizumab     |
| Berger [21]           | RCT          | UK      | 75          | 73              | 61.5 (9.9)            | 60.8 (10.2) | 0.5              | Focal/grid  | 3, 6, 9, 12                | Ranibizumab     |
| Ishibashi [19]        | RCT          | Japan   | 133         | 132             | 60.7 (9.37)           | 61.2 (10.52) | 0.5              | Focal/grid  | 3, 6, 12                  | Ranibizumab     |
| Liegl. [26]           | RCT          | Germany | 32          | 34              | 68.2 (11.3)           | 64.9 (11.6) | 0.5              | Grid        | 3, 6, 12                  | Ranibizumab     |
| Xu. [27]              | Retrospective study | China   | 31         | 30              | 60.9 (12.9)           | 62.0 (10.5) | 0.5              | Grid        | 3, 6, 9, 12                | Conbercept      |

*Age is given as the mean with the standard deviation in parenthesis.

**IVB** Intravitreal bevacizumab, **MPC** macular photocoagulation, **RCT** Randomized controlled trial, **VEGF** vascular endothelial growth factor
combination therapy with bevacizumab and MPC than in DME patients receiving monotherapy with bevacizumab. In addition, they showed that post-treatment CMT was lower at 6, 9 and 12 months in DME patients given combination therapy with ranibizumab and MPC than in DME patients given monotherapy with ranibizumab. Moreover, there were no significant differences in post-treatment BCVA at 1, 3, 6, 9 and 12 months between DME patients receiving combination therapy with an anti-VEGF agent (bevacizumab or ranibizumab) and MPC and those receiving monotherapy with an anti-VEGF agent.

The results of our meta-analysis also showed that post-treatment CMT at 3 months was lower in DME patients given combination therapy with bevacizumab and MPC than in those

Fig. 2 Forest plot of central macular thickness (CMT) comparing the two patient groups (DME patients given combination therapy with an anti-VEGF agent and MPC vs. those receiving monotherapy with an anti-VEGF agent) at 1, 3, 6, 9, 12, 18, 24, 30, 32 and 36 months of follow-up. Diamonds denote weighted mean difference (WMD) and 95% confidence interval (CI). Negative values indicate lower CMT in DME patients given combination therapy with an anti-VEGF agent and MPC than in DME patients receiving monotherapy with an anti-VEGF agent.

Fig. 3 Subgroup studies of CMT comparing patient groups (DME patients given combination therapy with an anti-VEGF agent and MPC vs. those receiving monotherapy with an anti-VEGF agent) receiving different kinds of anti-VEGF agents at 3 (a), 6 (b), 9 (c) and 12 (d) months of follow-up. Diamonds denote WMD and 95% CI. Negative values indicate lower CMT in DME patients given combination therapy with an anti-VEGF agent and MPC than in DME patients receiving monotherapy with an anti-VEGF agent.
receiving monotherapy with bevacizumab. This result is inconsistent with those reported by the authors of a recent meta-analysis who found no significant differences in post-treatment CMT between two groups of DME patients at 1, 3 and 6 months [17]. One explanation for this difference may be that the present meta-analysis included the recently published article of Das et al. [13] that was not included in the earlier meta-analysis. Das et al. [13] showed that the DME patient group receiving combination therapy had significantly lower post-treatment CMT at 3 and 6 months than did the DME patient group receiving monotherapy with intravitreal bevacizumab. Solaiman et al. [9] indicated that combined therapy with

Fig. 4 Subgroup studies of CMT comparing patient groups (DME patients given combination therapy with an anti-VEGF agent and MPC vs. those receiving monotherapy with an anti-VEGF agent) in studies with different designs (randomized controlled trial [RCT] vs. retrospective study) at 3 (a), 6 (b), 9 (c) and 12 (d) months of follow-up. Diamonds denote WMD and 95% CI. Negative values indicate lower CMT in DME patients given combination therapy with an anti-VEGF agent and MPC than in DME patients receiving monotherapy with an anti-VEGF agent

Fig. 5 Forest plot of best-corrected visual acuity (BCVA) comparing patient groups (DME patients given combination therapy with an anti-VEGF agent and MPC vs. those receiving monotherapy with an anti-VEGF agent) at 1, 3, 6, 9, 12, 18, 24, 30, 32 and 36 months of follow-up. Diamonds denote WMD and 95% CI. Negative values indicate lower BCVA in DME patients given anti-VEGF agents combined with MPC than in DME patients receiving monotherapy with an anti-VEGF agent.
| Study ID | WMD (95% CI) |
|---------|--------------|
| 1 month |              |
| Solaiman et al. (2010) | -0.95 (-1.58, -0.32) |
| Arevalo et al. (2013) | -0.04 (-0.27, 0.18) |
| Lee et al. (2011) | 0.15 (-0.23, 0.53) |
| Jovanovic et al. (2015) | -0.09 (-0.50, 0.39) |
| Subtotal (I-squared = 65.9%, p = 0.032) | -0.14 (-0.48, 0.19) |
| 3 months |              |
| K. Das et al. (2018) | 0.43 (-0.09, 0.94) |
| Solaiman et al. (2010) | -2.31 (-3.09, -1.53) |
| Arevalo et al. (2013) | -0.02 (-0.25, 0.20) |
| Lee et al. (2011) | 0.10 (-0.28, 0.48) |
| Nguyen et al. (2009) | -0.12 (-0.55, 0.31) |
| Berger et al. (2015) | -0.82 (-1.15, -0.48) |
| Ishibashi et al. (2015) | 0.14 (-0.10, 0.38) |
| Liegl et al. (2014) | -0.10 (-0.58, 0.38) |
| Xu et al. (2016) | 0.23 (-0.28, 0.73) |
| Subtotal (I-squared = 86.5%, p = 0.000) | -0.21 (-0.55, 0.13) |
| 6 months |              |
| K. Das et al. (2018) | 0.42 (-0.09, 0.93) |
| Solaiman et al. (2010) | -0.18 (-0.78, 0.42) |
| Arevalo et al. (2013) | -0.07 (-0.29, 0.16) |
| Lee et al. (2011) | 0.21 (-0.17, 0.60) |
| Herold et al. (2018) | 0.47 (-0.35, 1.28) |
| Berger et al. (2015) | -0.74 (-1.07, -0.41) |
| Ishibashi et al. (2015) | -0.03 (-0.27, 0.21) |
| Liegl et al. (2014) | -0.20 (-0.69, 0.28) |
| Xu et al. (2016) | 0.23 (-0.28, 0.73) |
| Subtotal (I-squared = 67.7%, p = 0.002) | -0.03 (-0.27, 0.20) |
| 9 months |              |
| Berger et al. (2015) | -0.34 (-0.67, -0.02) |
| Ishibashi et al. (2015) | 0.10 (-0.14, 0.34) |
| Xu et al. (2016) | 0.10 (-0.40, 0.61) |
| Subtotal (I-squared = 59.8%, p = 0.083) | -0.05 (-0.36, 0.26) |
| 12 months |              |
| Arevalo et al. (2013) | 0.00 (-0.23, 0.23) |
| Mitchell et al. (2011) | 0.69 (0.42, 0.95) |
| Herold et al. (2018) | -0.40 (-1.21, 0.41) |
| Berger et al. (2015) | -0.51 (-0.84, -0.19) |
| Ishibashi et al. (2015) | 0.02 (-0.22, 0.26) |
| Liegl et al. (2014) | -0.13 (-0.61, 0.36) |
| Xu et al. (2016) | 0.13 (-0.37, 0.63) |
| Subtotal (I-squared = 83.3%, p = 0.000) | 0.00 (-0.31, 0.32) |
| 18 months |              |
| Herold et al. (2018) | 0.15 (-0.65, 0.95) |
| Subtotal (I-squared = .%, p = .) | 0.15 (-0.65, 0.95) |
| 24 months |              |
| Arevalo et al. (2013) | -0.11 (-0.34, 0.12) |
| Herold et al. (2018) | -0.66 (-1.49, 0.16) |
| Subtotal (I-squared = 38.2%, p = 0.203) | -0.24 (-0.70, 0.22) |
| 30 months |              |
| Herold et al. (2018) | -0.55 (-1.37, 0.27) |
| Subtotal (I-squared = .%, p = .) | -0.55 (-1.37, 0.27) |
| 36 months |              |
| Herold et al. (2018) | -0.52 (-1.34, 0.29) |
| Subtotal (I-squared = .%, p = .) | -0.52 (-1.34, 0.29) |
| Overall (I-squared = 74.9%, p = 0.000) | -0.10 (-0.22, 0.02) |
bevacizumab and MPC was superior to monotherapy with bevacizumab in terms of reducing CMT at 3 and 6 months. Lee et al. [15] and Javanovic et al. [18] indicated no significant difference in post-treatment CMT at 1 month between DME patients given combination therapy with bevacizumab and MPC and those receiving monotherapy with bevacizumab. Arevalo et al. [14] showed no significant difference in post-treatment CMT between the two DME patient groups at 1, 3 and 6 months. No recent meta-analysis has compared CMT in DME patients receiving monotherapy with ranibizumab and those receiving combination therapy with ranibizumab and MPC. Ishibashi et al. [19] reported that post-treatment CMT was lower in DME patients receiving combination therapy with ranibizumab and MPC at 6, 9 and 12 months than in those receiving monotherapy with ranibizumab. Mitchell et al. [20] indicated no significant difference in post-treatment CMT between the two groups of DME patients at 12 months. Berger et al. [21] showed that combined therapy with ranibizumab and

### Fig. 6 Subgroup studies of BCVA comparing groups (DME patients given combination therapy with an anti-VEGF agent and MPC vs. those receiving monotherapy with an anti-VEGF agent) receiving different kinds of anti-VEGF agents at 3 (a), 6 (b) and 12 (c) months. Diamonds denote WMD and 95% CI. Negative values indicate lower BCVA in DME patients given anti-VEGF agents combined with MPC than in DME patients receiving monotherapy with an anti-VEGF agent.
MPC was superior to monotherapy with ranibizumab in terms of CMT reduction at 12 months, whereas there was no significant difference in post-treatment CMT between the two groups of DME patients at 3, 6 and 9 months. Our meta-analysis showed that CMT was lower at 6, 9 and 12 months of follow-up in DME patients given combination therapy with ranibizumab and MPC than in those receiving monotherapy with an anti-VEGF agent; however, the difference disappeared after 12 months of follow-up. CMT is an index that represents the anatomic change in DME levels. The better results in DME patients receiving combination therapy with an anti-VEGF agent and MPC indicate that MPC had a transiently synergistic effect in decreasing the level of DME when used in combination with an anti-VEGF agent. A relatively longer follow-up was essential to be able to evaluate the long-term existence of the synergistic effect.

In contrast, the meta-analysis showed no significant differences in BCVA at 1, 3, 6, 9 and 12 months of follow-up between DME patients receiving combination therapy with an anti-VEGF agent and MPC and those receiving monotherapy with an anti-VEGF agent.
monotherapy with an anti-VEGF agent. This result corresponds to the findings of a recent meta-analysis [17] that showed no difference in BCVA at 1, 3 and 6 months of follow-up between DME patients receiving combination therapy with bevacizumab and MPC and those receiving monotherapy with bevacizumab. This absence of any difference between the two groups did not parallel the corresponding changes in CMT in the eyes of the two patient groups, possible due to the many factors that can influence the visual outcome. Such factors include the severity and duration of macular edema, age of the patient, status of the macula before the onset of edema and presence of foveal hard exudates [22, 23]. These results support our finding of no synergistic effect of combined therapy with an anti-VEGF agent and MPC on BCVA.

There are some limitations to our study. First, the number of included studies was limited in order to explore the sources of heterogeneities. Second, some studies did not adjust for common confounding variables (the degree of glycemic control and level of serum lipids), which may have had an influence on the results of the meta-analysis.

CONCLUSIONS

In conclusion, the results of the present meta-analysis demonstrate a transiently synergistic effect of MPC on CMT when used in combination with an anti-VEGF agent, whereas no similar synergistic effect could be detected on BCVA. Also, a relatively longer follow-up was essential to be able to evaluate the existence of the synergistic effect.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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