Clinical effectiveness of ranibizumab and conbercept for neovascular age-related macular degeneration: a meta-analysis

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Introduction: To assess the ocular efficacy of intravitreal ranibizumab and conbercept injection in patients with neovascular age-related macular degeneration.

Materials and methods: We searched PubMed, Web of Science, Cochrane Library, EMBASE, Google Scholar, Medline, China National Knowledge Infrastructure, and WANFANG DATA databases, up to June 20, 2018. We also searched abstracts and clinical study presentations at meetings as well as trial registries; we contacted authors of included studies if questions arose. Eligibility criteria for selection of studies were randomized controlled trials and retrospective trials that compared ranibizumab with conbercept for treatment of neovascular age-related macular degeneration.

Results: Eight randomized controlled trials and four retrospective studies were included with a total of 853 patients. Best-corrected visual acuity after loading dosage was improved in the conbercept group, compared with the ranibizumab group (weighted mean difference: −0.04; 95% CI: −0.07 to 0.00; P=0.04). There was a significant difference between conbercept and ranibizumab therapy with respect to unchanged or recurrent leakage of choroidal neovascularization (OR: 0.46; 95% CI: 0.24–0.88; P=0.02). No significant differences were observed in central macular thickness (weighted mean difference: −2.92; 95% CI: −9.00 to 3.17; P=0.35), complete and partial closure of leakage of choroidal neovascularization (complete closure, P=0.70; partial closure, P=0.35), or number of injections (weighted mean difference: 0.42; 95% CI: −0.46 to 1.29; P=0.35) between the conbercept and ranibizumab groups at the end of the follow-up periods.

Conclusion: Pooled evidence confirmed that conbercept was superior to ranibizumab with respect to visual gain after treatment. Additional studies with long-term follow-up are needed to support our conclusion.

Keywords: age-related macular degeneration, best-corrected visual acuity, central macular thickness, choroidal neovascularization, vision loss

Introduction

Age-related macular degeneration (AMD), which comprises 8.7% of all cases of blindness, is the third leading cause of irreversible vision loss worldwide and the most common cause of blindness in people over 50 years of age.1 Advanced AMD includes neovascular (wet or exudative) AMD (nAMD), which is characterized by choroidal neovascularization (CNV) and proliferation of fibrous tissue.2 Notably, wet AMD constitutes 10%–15% of all cases of AMD but is responsible for >90% of severe visual loss from AMD.3 Patients with nAMD can experience sudden and severe central vision loss within days or weeks, primarily caused by CNV.4–6 Vascular endothelial growth factor (VEGF) has been identified as a principle mediator of CNV in the pathogenesis...
of AMD. Thus far, the application of anti-VEGF drugs has been the mainstay of nAMD treatment. Anti-VEGF agents, including ranibizumab (Lucentis®, Genentech Inc., South San Francisco, CA, USA), bevacizumab, and aflibercept, substantially reduce visual loss in the treatment of nAMD.7

Ranibizumab is a recombinant, humanized, monoclonal immunoglobulin G1 (IgG1) k isotype antibody antigen-binding fragment (Fab), which can neutralize all isoforms of VEGF-A. It was approved for the treatment of nAMD by the US Food and Drug Administration (FDA) in 2006.5-10 The newest anti-VEGF drug, conbercept (or KH902, Lumitin, Chengdu Kang Hong Biotech Co, Ltd., Sichuan, People’s Republic of China), is a recombinant fusion protein composed of extracellular domain 2 of VEGFR-1 and extracellular domains 3 and 4 of VEGFR-2 (KDR-d4), combined with the Fc portion of human IgG1. Conbercept is similar in structure to aflibercept, an anti-VEGF agent that binds to all isoforms of VEGF-A, VEGF-B, and placent growth factor (PIGF); additionally, conbercept exhibits a higher affinity to VEGF because of the addition of the fourth Ig-like domain of VEGFR-2 in the Fab fragment.11

In clinical practice, conbercept is effective in some patients who are nonresponsive to ranibizumab and bevacizumab.12,13 In preclinical trials, the binding affinity of conbercept for VEGF was reported to be significantly greater than that of ranibizumab.14 Conbercept was approved for the treatment of nAMD by the China State FDA in December 2013. However, the drug has not yet reached other markets. This meta-analysis aimed to compare the ocular efficacy of conbercept and ranibizumab in the treatment of nAMD from the perspective of studies from People’s Republic of China.

Materials and methods

Literature search

A systematic search was performed to identify relevant studies comparing ranibizumab with conbercept for the treatment of nAMD by using the following databases: PubMed, Wed of Science, Cochrane Library, EMBASE, Google Scholar, Medline, China National Knowledge Infrastructure, and WANFANG DATA. The search included all published trials up to June 20, 2018, with the following Medical Subject Heading terms: “Macular Degeneration or Age-Related Macular Degeneration or AMD or ARMD or nAMD,” and “ranibizumab or Lucentis,” and “conbercept or KH902 or Lumitin.” No language restrictions were used in the search. Furthermore, the “related articles” function was used to broaden the search, and all relevant studies were included for further screening.

Inclusion criteria and exclusion criteria

Trials were included if they met the following criteria: 1) randomized controlled trials (RCTs) and/or non-RCTs, 2) studies that included the comparison of ranibizumab with conbercept, 3) patients with AMD that required anti-VEGF therapy, and 4) studies that included at least one outcome of interest mentioned below with relative data reported or able to be calculated: number of injections of ranibizumab and conbercept, best-corrected visual acuity (BCVA), and central macular thickness (CMT) on optical coherence tomography. Trials were excluded if any of the following conditions were met: 1) patients had other diseases, such as diabetic retinopathy, 2) no outcomes of interest were reported, or calculating or extrapolating the necessary data for either ranibizumab or conbercept from the published results was impossible, and/or 3) reports were duplicated.

Data extraction and outcomes of interest

Two independent reviewers (RH and LPW) searched the literature, assessed the quality of trials, and extracted the following data with a standardized form: first author name, year of publication, country, study interval, study design, number of patients who underwent ranibizumab or conbercept therapy, follow-up duration, and outcomes of interest. All BCVA values were converted into log minimum angle of resolution (ie, LogMAR) for analysis. All discrepancies regarding eligibility and data extraction were resolved by discussion among all authors until a consensus was reached.

Study quality and level of evidence

The levels of evidence of included studies were rated by two reviewers, according to criteria used by the Centre for Evidence-Based Medicine in Oxford, UK.15 The reviewers independently assessed the quality of the studies, and any disagreement was resolved by consensus.

Statistical analyses

The present meta-analysis was conducted according to the recommendations of the Cochrane Collaboration, as well as the Quality of Reporting of Meta-analyses guidelines.16 All the statistical analyses were performed by using RevMan 5.3 (Cochrane Library Software, Oxford, UK). Weighted mean differences (WMDs) were used for continuous variables; odds ratios (ORs) were used for dichotomous variables. The CIs were set at 95%.

All pooled estimates were determined by using the z test; P-values <0.05 were considered statistically significant. The degree of heterogeneity among included studies was assessed by using the chi-squared-based Q test and the F test;
heterogeneity was defined by $I^2>50\%$ and $P<0.05$. When the evidence indicated that interstudy heterogeneity existed, a random-effects model was used; otherwise, a fixed-effects model was adopted. Sensitivity analysis was performed by omission of specific studies. Variables were pooled when outcomes were reported by three or more studies in the overall meta-analysis. Publication bias was assessed by using a funnel plot.

**Results**

**Literature review process**

After screening, a total of 12 studies with a total of 853 participants were included in the present meta-analysis. The studies included eight RCTs and four retrospective studies; 433 and 420 patients received injections of ranibizumab and conbercept, respectively. Figure 1 shows a flow diagram of the study procedure; Table 1 shows the characteristics of the included studies.

**BCVA**

No significant difference was observed in BCVA before treatment between the conbercept and ranibizumab groups (WMD: 0.01; 95% CI: −0.02 to 0.03; $P=0.65$). However, after 3 months treatment with conbercept or ranibizumab, BCVA significantly differed between the two groups (WMD: −0.04; 95% CI: −0.07 to 0.00; $P=0.04$). Studies by Cai and Peng and Cui et al were not included because they only showed improvement of vision, rather than BCVA, after treatment with conbercept or ranibizumab. Patients treated with monthly injections of conbercept experienced greater improvement of BCVA from baseline compared with patients treated with ranibizumab. Figure 2 shows the source data describing changes of BCVA in the included studies.

**CMT**

Average CMTs were detected on optical coherence tomography images at the start and end of the follow-up period in the conbercept and ranibizumab groups. No significant differences were observed in the average CMT before treatment (WMD: −2.62; 95% CI: −9.92 to 4.68; $P=0.48$) and after treatment (WMD: −2.92; 95% CI: −9.00 to 3.17; $P=0.35$) between the conbercept and ranibizumab groups (Figure 3).

**Leakage of CNV**

No significant differences were observed in the rate and degree of CNV recovery between the conbercept and ranibizumab groups, in complete closure (OR: 1.10; 95% CI: 0.68–1.79; $P=0.70$) or partial closure (OR: 1.26; 95% CI: 0.78–2.03; $P=0.35$) (Figure 4). However, there was a significant difference between the two groups in unchanged or recurrent leakage of CNV (OR: 0.46; 95% CI: 0.24–0.88; $P=0.02$) (Figure 4).

**Number of injections**

No statistical difference was observed in the mean number of injections between the conbercept and ranibizumab groups (WMD: 0.42; 95% CI: −0.46 to 1.29; $P=0.35$) (Figure 5).

**Sensitivity analysis and publication bias**

Heterogeneity was apparent in injection numbers ($P=0.00001$, $I^2=94\%$). Therefore, sensitivity analysis was performed, in
which specific studies were omitted and the remaining studies were analyzed to determine whether the results could have been markedly affected by a single study. Sensitivity analyses suggested that no individual study significantly affected the overall estimate of the numbers of injections. We concluded that the reasons for heterogeneity, other than clinical differences, such as different treatment regimens, could include small sample size, which was inadequate to accurately estimate heterogeneity. No significant heterogeneity was observed in the remaining seven measures (BCVA before treatment: $\chi^2=1.85, df=4, P=0.76, I^2=0\%$; BCVA after treatment: $\chi^2=3.87, df=4, P=0.42, I^2=0\%$; CMT before treatment: $\chi^2=2.64, df=10, P=0.99, I^2=0\%$; CMT after treatment: $\chi^2=9.13, df=9, P=0.43, I^2=1\%$; complete closure of leakage of CNV: $\chi^2=1.40, df=3, P=0.71, I^2=0\%$; partial closure of leakage of CNV: $\chi^2=1.18, df=3, P=0.76, I^2=0\%$). A funnel

Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study interval</th>
<th>Study design</th>
<th>LOE*</th>
<th>Treatment regimen</th>
<th>Number of patients, conbercept/ ranibizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cui et al.2018</td>
<td>People’s Republic of China</td>
<td>2014–2015</td>
<td>Retrospective</td>
<td>2b</td>
<td>As-needed</td>
<td>83/85</td>
</tr>
<tr>
<td>Huang et al.2018</td>
<td>People’s Republic of China</td>
<td>2013–2016</td>
<td>Retrospective</td>
<td>2b</td>
<td>Monthly for 3 months then as-needed</td>
<td>35/44</td>
</tr>
<tr>
<td>Li et al.2018</td>
<td>People’s Republic of China</td>
<td>2016–2017</td>
<td>RCT</td>
<td>2b</td>
<td>Monthly for 3 months then as-needed</td>
<td>20/20</td>
</tr>
<tr>
<td>Lv et al.2016</td>
<td>People’s Republic of China</td>
<td>2013–2015</td>
<td>RCT</td>
<td>2b</td>
<td>Monthly for 3 months then as-needed</td>
<td>42/42</td>
</tr>
<tr>
<td>Zhao and Bai.2017</td>
<td>People’s Republic of China</td>
<td>2013–2014</td>
<td>Retrospective</td>
<td>2b</td>
<td>Monthly for 3 months then as-needed</td>
<td>30/31</td>
</tr>
</tbody>
</table>

Note: Based on US Preventive Services Task Force grading system.
Abbreviations: LOE, level of evidence; RCT, randomized control trial.

Figure 2 Forest plot and meta-analysis of BCVA.
Notes: (A) BCVA before treatment; (B) BCVA after treatment.
Abbreviation: BCVA, best-corrected visual acuity.
### A

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Conbercept Mean (SD)</th>
<th>Ranibizumab Mean (SD)</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cai X 2016</td>
<td>394.67 (121.1)</td>
<td>381 (108.32)</td>
<td>30</td>
<td>1.6</td>
</tr>
<tr>
<td>Cui J 2017</td>
<td>215.3 (42.5)</td>
<td>220.7 (36.8)</td>
<td>85</td>
<td>36.8</td>
</tr>
<tr>
<td>Huang Z 2018</td>
<td>407 (146)</td>
<td>394 (93)</td>
<td>35</td>
<td>1.9</td>
</tr>
<tr>
<td>Lv P 2016</td>
<td>338.6 (46.4)</td>
<td>341.5 (57.3)</td>
<td>42</td>
<td>10.7</td>
</tr>
<tr>
<td>Niu J 2016</td>
<td>381.5 (81.5)</td>
<td>390.7 (79.5)</td>
<td>20</td>
<td>2.1</td>
</tr>
<tr>
<td>Yang J 2018</td>
<td>389.6 (62.6)</td>
<td>388.9 (65.8)</td>
<td>24</td>
<td>4.0</td>
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<tr>
<td>Zhang H 2016</td>
<td>237.82 (27.96)</td>
<td>236.59 (28.64)</td>
<td>25</td>
<td>21.6</td>
</tr>
<tr>
<td>Zhang L 2017</td>
<td>411.4 (62.3)</td>
<td>414 (93.1)</td>
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<td>Zhang Z 2017</td>
<td>389.6 (62.6)</td>
<td>388.9 (65.8)</td>
<td>49</td>
<td>8.2</td>
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<tr>
<td>Zhao Y 2015</td>
<td>327.1 (51.5)</td>
<td>348.9 (73.4)</td>
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<td>5.3</td>
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<td>Zheng M 2017</td>
<td>347.82 (73.18)</td>
<td>346.82 (73.63)</td>
<td>43</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Total (95% CI): 409

Heterogeneity: $\chi^2=2.64$, df=10 (P=0.99); I=0%

Test for overall effect: Z=0.70 (P=0.48)

### B

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Conbercept Mean (SD)</th>
<th>Ranibizumab Mean (SD)</th>
<th>Total Weight (%)</th>
<th>Mean difference IV, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cai X 2016</td>
<td>246.33 (81.09)</td>
<td>228.33 (65.35)</td>
<td>30</td>
<td>2.7</td>
</tr>
<tr>
<td>Cui J 2017</td>
<td>215.3 (42.5)</td>
<td>220.7 (36.8)</td>
<td>85</td>
<td>25.5</td>
</tr>
<tr>
<td>Huang Z 2018</td>
<td>230 (71)</td>
<td>208 (56)</td>
<td>35</td>
<td>4.7</td>
</tr>
<tr>
<td>Lv P 2016</td>
<td>309.6 (37)</td>
<td>307.1 (40.6)</td>
<td>42</td>
<td>13.4</td>
</tr>
<tr>
<td>Niu J 2016</td>
<td>343.5 (64.2)</td>
<td>342.8 (65.3)</td>
<td>20</td>
<td>2.3</td>
</tr>
<tr>
<td>Yang J 2018</td>
<td>341 (42.1)</td>
<td>341.2 (44.6)</td>
<td>24</td>
<td>6.1</td>
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<tr>
<td>Zhang H 2016</td>
<td>180.76 (26.34)</td>
<td>196.56 (25.51)</td>
<td>25</td>
<td>18.6</td>
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<tr>
<td>Zhang L 2017</td>
<td>292.6 (53.5)</td>
<td>309.3 (49.5)</td>
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<td>3.6</td>
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<tr>
<td>Zhang Z 2017</td>
<td>342.7 (43.2)</td>
<td>342.2 (43.8)</td>
<td>49</td>
<td>12.5</td>
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<tr>
<td>Zhao Y 2015</td>
<td>310 (57.2)</td>
<td>306.3 (73.7)</td>
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<td>3.4</td>
</tr>
<tr>
<td>Zheng M 2017</td>
<td>306.22 (53.12)</td>
<td>306.64 (54.13)</td>
<td>43</td>
<td>7.1</td>
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</tbody>
</table>

Total (95% CI): 409

Heterogeneity: $\chi^2=9.18$, df=10 (P=0.51); I=0%

Test for overall effect: Z=0.94 (P=0.35)

### Figure 3

Forest plot and meta-analysis of CMT.

**Notes:** (A) CMT before treatment; (B) CMT after treatment.

**Abbreviation:** CMT, central macular thickness.

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In People’s Republic of China, conbercept has been widely used as the first-line drug for the treatment of nAMD for nearly 5 years. Therefore, the systemic effects of conbercept during treatment of nAMD require great attention. The efficacies of ranibizumab and conbercept for nAMD have been reported separately by different groups; both drugs have been shown to significantly improve visual acuity in patients with nAMD.licking other papers, however, these data have not been systematically sorted, collected, and assessed. The present study provided further information regarding the ocular efficacy of conbercept and ranibizumab from a clinical perspective.

In this meta-analysis, no significant differences were noted in BCVA and CMT before treatment, which indicated that conbercept and ranibizumab cohorts showed no significant differences in baseline parameters. Interestingly, BCVA was significantly better in the conbercept group than in the ranibizumab group at the end of the follow-up period. Conbercept is similar to the anti-VEGF agent aflibercept (Eylea®, Regeneron Pharmaceuticals, Eastview, NY, USA), which binds to all isoforms of VEGF-A, VEGF-B, and PI GF. Indeed, this result is consistent with a study by Inoue et al, which reported superior BCVA at 6 months, compared with baseline, after aflibercept treatment. Additionally, Huang et al reported no significant difference in the visual improvement of patients with polypoidal choroidal vasculopathy between the conbercept and ranibizumab groups at 6 months; however, conbercept was superior to ranibizumab monotherapy in the regression of polyps. Moreover, Cui et al confirmed that conbercept and ranibizumab showed equivalent effects with respect to visual gain and reduction of central retinal thickness at 1 year, when administered according to a treat-and-extend protocol.

The above results confirmed superior BCVA after treatment in the conbercept group, compared with that in the ranibizumab group. However, no significant differences were observed in CMT between the two groups. The results of BCVA analysis seemed to be inconsistent with those...
of CMT analysis. This inconsistency could be because CMT and BCVA are affected by the morphology, size, and level of macular edema, as well as the disruption of photoreceptors.31 The precursors of hard exudates in cysts located in the outer nuclear layer32 can invade the external limiting membrane and photoreceptors, resulting in photoreceptor degeneration and apoptosis;33 hydraulic pressure in the cysts also exerts an impact on the external limiting membrane and photoreceptors.33 Malfunctional Müller cell-derived VEGF causes pathological permeability of the barrier in the sensory retina under hypoxic or ischemic conditions.34 Pelosini et al35 concluded that the integrity of the cross-sectional area of retinal tissue between the plexiform layers in cystoid macular edema has a linear relationship

Figure 4 Forest plot and meta-analysis of leakage of CNV.
Notes: (A) Complete closure; (B) partial closure; (C) no change and recurrent exudative activity.
Abbreviation: CNV, choroidal neovascularization.

Figure 5 Forest plot and meta-analysis of the number of injections.
Notes: Experimental group: conbercept; control group: ranibizumab.
of multiple targets of VEGFR, and so it is reasonable to speculate that it might exhibit a longer duration of action. The concentrations of conbercept in the rabbit retina and choroid remained higher than the in vitro 50% inhibitory concentration value (7 ng/g) over 34 days, indicating that a single 0.5 mg intravitreal injection may have an inhibitory effect against VEGF over the course of 81 days.

Moreover, domain 4 of VEGFR-2 exhibits a lower isoelectric point (PI). A prior study showed that a high positive charge of a fusion protein may lead to poor pharmacokinetic properties. The introduction of domain 4 of conbercept may enhance its association with VEGF and prolong the half-life of the drug.

The current study has several limitations. First, conbercept has only recently been applied in clinical practice. Therefore, the data available from People’s Republic of China are limited; this was our reason for inclusion of both RCTs and retrospective studies. Further studies with long-term follow-up periods and reports of curative effects are required to confirm whether the improvement in visual acuity at different time points as well as improvements in various anatomical outcomes are maintained over time. Second, further clinical research is required to compare the efficacy of conbercept with structurally similar anti-VEGF drugs, such as aflibercept (Eylea®), which has recently become commercially available in People’s Republic of China. Moreover, personalized treatment also must be considered and thoroughly explored.

Conclusion
The results of this meta-analysis indicate that both conbercept and ranibizumab are effective choices for the treatment of AMD, although conbercept is superior with respect to visual gain.

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Author contributions
All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.
Disclosure

The authors report no conflicts of interest in this work.

References

