Anti-VEGF Monotherapy Versus Photodynamic Therapy and Anti-VEGF Combination Treatment for Neovascular Age-Related Macular Degeneration: A Meta-Analysis

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PURPOSE. The purpose of this study was to compare the efficacy and safety of anti-VEGF monotherapy with verteporfin photodynamic therapy (PDT) and anti-VEGF combination treatment in neovascular AMD.

METHODS. This study used a meta-analysis of randomized controlled trials.

RESULTS. We included a total of 16 studies that included 587 patients in the monotherapy group and 673 in the combination treatment group. There was no statistical difference between best corrected visual acuity (BCVA) and central retinal thickness (CRT) at end of the study and the proportions of patients who gained ≥15 BCVA letters between the two treatment groups. Nevertheless, combination therapy required fewer anti-VEGF injections than monotherapy. Subgroup analyses showed that CRT at end of the study was thinner in the standard-fluence (SF) PDT combination therapy group than in the monotherapy group (weighted mean difference [WMD]: 17.256; 95% confidence interval [CI]: 5.423~29.089; P = 0.004). The reduced-fluence (RF) PDT combination therapy group required fewer anti-VEGF injections than the monotherapy group (WMD: 3.217; 95% CI: 2.798~3.636; P < 0.001), while the number of anti-VEGF treatments between the SF PDT combination therapy and monotherapy groups was not statistically different (WMD: 0.23; 95% CI: -0.016~0.475; P = 0.067). In the combination therapy group, there was no difference between the PDT + anti-VEGF versus anti-VEGF retreatment regimens.

CONCLUSIONS. This study indicates that verteporfin PDT and anti-VEGF combination therapy is effective for achieving BCVA gain and CRT reduction comparable with that of anti-VEGF monotherapy. Combination therapy with RF PDT can potentially decrease the number of anti-VEGF injections needed.

Keywords: age-related macular degeneration, anti-vascular endothelial growth factor, photodynamic therapy, meta-analysis

In developed countries, AMD is one of the leading causes of visual impairment and blindness in elderly individuals.1,2 The most common cause of vision loss is the development of choroidal neovascularization (CNV), the typical characteristic of neovascular AMD (nAMD). CNV underneath the fovea leads to choroidal hemorrhage and retinal swelling, giving rise to central visual blurring, distortion, or scotomas, which have a profound impact on patients’ lives.

The upregulation of VEGF results in CNV by stimulating vascular endothelial cell proliferation and disrupting endothelial cell tight junctions, consequently increasing vascular permeability.3 Anti-VEGF injections have been established as the standard therapy for CNV and nAMD, where constant treatment appears necessary.4 Repeated injections are required to slow the growth of new abnormal blood vessels and improve visual function. The need for frequent injections not only imposes a significant burden on patients and health care systems, but it also leads to increased potential infection risk for patients with nAMD.5,6

Before the use of anti-VEGF therapy in nAMD, photodynamic therapy (PDT) was the main treatment approach for patients. Verteporfin, a photosensitizing drug, accumulates preferentially in CNV. Verteporfin photoactivation generates reactive oxygen species that cause changes to local endothelial cells. This triggers platelet binding and aggregation, leading to neovascular thrombosis formation and CNV closure.6 Several studies have demonstrated the efficacy and safety of verteporfin PDT in nAMD.7 However, anti-VEGF therapy has better efficacy for improving final best corrected visual acuity (BCVA) than does verteporfin PDT in AMD.6,9 Moreover, verteporfin PDT may affect the choriocapillaris bed surrounding the pathologic CNV lesion and may lead to hypoxia, thereby indirectly upregulating VEGF and stimulating further CNV growth.10

Anti-VEGF therapy targets key mediators of the angiogenic cascade, whereas verteporfin targets the vascular component. Their different working mechanisms on CNV potentially have additive or synergistic effects on combination therapy. In addition, antiangiogenic agents may counteract the upregulation of VEGF after verteporfin PDT. To date, whether combination therapy is superior to anti-VEGF monotherapy in nAMD remains controversial. Furthermore, the effects of verteporfin PDT of different fluences on combination treatment...
Anti-VEGF vs. PDT + Anti-VEGF in nAMD: Meta-Analysis

are unknown. To explore the best therapy for nAMD, we performed a meta-analysis to compare mono-therapy with combination treatment. Subgroup analyses related to verteporfin PDT of different fluences and retreatment regimens in combination therapy were performed to explore the underlying factors affecting final outcomes.

METHODS

This meta-analysis was performed strictly according to a protocol established before the start of the literature search and data analysis. The study was carried out and reported based on the preferred reporting items for systematic reviews and meta-analyses statement.12

Search Strategy

Literature published prior to July 2017 was searched in PubMed, Web of Science, and Cochrane Library databases using the following keywords or corresponding medical subject headings: macular degeneration, wet macular degeneration, Visudyne, PDT, photon dynamic, photodynamic, photocoagulation, vascular endothelial growth factors, anti-vascular endothelial growth factors, anti-VEGF, angiongenesis inhibitors, endothelial growth factors, angiongenesis-inducing agents, Macugen, pegaptanib, bevacizumab, Avastin, rhuFab, Lucentis, ranibizumab, conbercept, aflibercept. All related articles were retrieved without language or geographic limitations. The reference lists of the relevant articles were manually examined to identify other potentially related studies. Trial registries were also checked for unpublished studies.

Eligibility Criteria

All included studies met the following criteria: (1) study design: randomized controlled trial (RCT); (2) population: patients with active CNV secondary to AMD; (3) intervention: combined anti-VEGF therapy and PDT versus anti-VEGF monotherapy; (4) outcome variables: BCVA, central retinal thickness (CRT), number of anti-VEGF treatments, proportion of patients who gained ≥15 BCVA letters at end of the study. The exclusion criteria were (1) follow-up <6 months; (2) duplicate publications; (3) letters, review articles; (4) cadaver subjects or animal studies.

Data Extraction and Quality Assessment

After initial systematic screening of articles based on the abstract and titles, the full texts of each article were obtained and reviewed. We included articles that met the eligibility criteria and that failed the exclusion criteria. Two reviewers (YG and TY) independently screened the studies and extracted data from the articles. Disagreements were calculated using Cohen’s k coefficient and resolved by consensus and discussion with the corresponding author (GD). We extracted the study characteristics and results of eligible studies, including (1) basic data (name of the first author, publication year, location, design, follow-up time, comparability of groups, sample size, patient age, sex ratio) and (2) outcomes (BCVA and CRT at baseline and the end of the study, number of treatments at end of the study; the proportion of patients who gained ≥15 BCVA letters at end of the study, the ratio of cases with adverse events such as eye pain, reduced visual acuity, endophthalmitis, arterial thromboembolic events). The corresponding authors of the retrieved articles were contacted if additional data were needed. Two reviewers (YG and YZ) independently assessed the included trials for bias according to the methods described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions.12 The following parameters were assessed: sequence generation; allocation concealment; masking (blinding) of participants, personnel, and outcome assessors; incomplete outcome data; and selective outcome reporting. We evaluated these parameters for each outcome measure or class of outcome measure, and classified each parameter as low risk of bias, high risk of bias, or unclear risk of bias.

Data and Subgroup Analyses

Statistical analyses were performed with statistical software (Stata/SE 12.0; StataCorp, College Station, TX, USA). The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated for continuous data; the relative risk (RR) and 95% CI were calculated for dichotomous data. We conducted meta-analyses using random-effects models, unless there were fewer than three trials that contributed outcome data for a meta-analysis, in which case we used a fixed-effect model. Statistical heterogeneity was tested by the χ² and I² tests. If heterogeneity was substantial (P < 0.1, I² > 50%), sensitivity analysis was performed to identify the source of the heterogeneity. If the heterogeneity could not be eliminated, a random-effect model was used when the meta-analysis result had clinical homogeneity, or a descriptive analysis was used. Publication bias was assessed using Begg’s funnel plot and Egger’s linear regression test. For all statistical analyses, except for heterogeneity, P < 0.05 was considered to indicate statistical significance.

Subgroup analyses were performed based on the following factors: verteporfin PDT of different fluences in combination therapy (i.e., standard-fluence [SF] versus reduced-fluence [RF]), retreatment regimen of combination therapy (PDT + anti-VEGF versus anti-VEGF), previous CNV treatment, and lesion type. The results are reported as forest plots of the effect size with the 95% CI.

RESULTS

Overall Characteristics of Selected Trials and Quality Assessment

A total of 510 relevant articles were initially identified for this meta-analysis. After removing duplicates, 28 articles were considered potentially eligible based on the title and abstract. After reviewing the full texts of these articles, 12 studies were excluded for unrelated or insufficient data. Finally, a total of 16 studies from 2010 to 2017 were selected for this meta-analysis.13–28 Figure 1 shows the flow diagram of the search procedure and results. Table 1 presents the characteristics of the included studies. Among the 16 studies, seven were conducted in Europe,14,15,17,21,24–26 four in the United States,13,16,19,26 and three in Australia.18,20,27 Only three studies enrolled patients with previous CNV treatment,18,22,24 and previous treatment had been at least 30 days before enrollment. The studies included a total of 1260 participants who were divided into the anti-VEGF monotherapy group (587 patients) and PDT + anti-VEGF combination therapy group (673 patients). The intervention of the combination therapy group was 50 J/cm² SF PDT and anti-VEGF treatment in seven studies17,18,20,22-23,27 and was 25 J/cm² RF verteporfin PDT and anti-VEGF treatment in six studies.14–16,25–27 The retreatment regimen in the combination therapy group referred to PDT + anti-VEGF in seven articles,16,17,19,21,23,24,28 and the remaining nine articles referred to anti-VEGF treatment.13–15,18,20,22–27 Thirteen trials were followed-up for 12 months, one trial was
followed-up for 24 months, and two trials were followed-up for 6 months. Eleven studies compared ranibizumab monotherapy with ranibizumab + PDT combination treatment. Seven studies compared bevacizumab monotherapy with bevacizumab + PDT combination therapy. Details of the risk of bias assessment are provided in Figure 2, which presents a summary. There was excellent interrater agreement regarding eligibility ($\kappa = 0.78$).

**Best Corrected Visual Acuity**

Seven studies that included 316 patients in the monotherapy group and 317 patients in the combination therapy group reported the BCVA (Early Treatment Diabetic Retinopathy Study [EDTRS] scale) at baseline, for which a random-effect model was used ($P = 0.390$, $I^2 = 4.9\%$). The pooled result showed no statistical difference between the baseline BCVA of the two groups ($WMD = 1.672$, 95% CI: $-3.959$ to $0.735$, $P = 0.178$, Table 2).

Nine studies with 403 patients in the monotherapy group and 480 patients in the combination therapy group reported the BCVA at the end of the study. A random-effect model was chosen ($P = 0.083$, $I^2 = 42.7\%$). There was no statistical difference between the end-of-study BCVA of the two groups ($WMD = 1.928$, 95% CI: $-1.495$ to $5.352$, $P = 0.270$, Table 2).

We also analyzed the proportion of patients who gained $\geq 15$ BCVA letters at the end of the study, which was reported in 10 trials that included 445 patients in the monotherapy group and 433 patients in the combination therapy group. A random-effect model was used ($P = 1.000$, $I^2 = 0.0\%$). Monotherapy was associated with a higher ratio of patients who gained $\geq 15$ BCVA letters as compared to combination treatment. However, the pooled result revealed no statistical difference between the two groups (RR = 0.948, 95% CI: 0.890 to 1.009, $P = 0.095$).

**Central Retinal Thickness**

Twelve studies that included 432 patients in the monotherapy group and 420 patients in the combination therapy group reported the CRT at baseline. As with BCVA, a random-effect model was used ($P = 0.818$, $I^2 = 0.0\%$). The pooled result...
revealed no statistical difference between the two groups (WMD = -5.209, 95% CI: -18.979 to 8.560, P = 0.458, Table 3). Thirteen studies with 520 patients in the monotherapy group and 608 patients in the combination therapy group reported the CRT at the end of the study. A random-effect model was used (P = 0.059, I^2 = 42.5%). The result did not show a significant difference between the end-of-study CRT of the two groups (WMD = 2.906, 95% CI: -6.205 to 12.017, P = 0.532, Table 3).

**Table 1.** The Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>First Author</th>
<th>Publication Year</th>
<th>Location</th>
<th>Previous CNV Treatment</th>
<th>Design</th>
<th>Follow-up, mo</th>
<th>Groups</th>
<th>Sample Size</th>
<th>Average Age, y</th>
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<td>Larsen, M.</td>
<td>2012</td>
<td>Europe</td>
<td>Naive</td>
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<td>IVR(3+PRN)+sham PDT 133</td>
<td>75.5 ± 7.4</td>
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<td></td>
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<td>IVR(3+PRN)+SF PDT 122</td>
<td>76.8 ± 7.7</td>
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<td>Kaiser, P.K.</td>
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<td>Naive</td>
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<td>IVR(3+PRN)+sham PDT 112</td>
<td>NR</td>
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<td>IVR(3+PRN)+SF PDT 104</td>
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<td>IVR(3+PRN)+RF PDT 105</td>
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<td>RCT</td>
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<td>IVR(3+PRN)+40% PDT 29</td>
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<td>Gallemore, R.P.</td>
<td>2017</td>
<td>USA</td>
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<td>RCT</td>
<td>24</td>
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<td>IVR(3+PRN)+RF PDT 45</td>
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<td>Hatz, K.</td>
<td>2015</td>
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<td>No laser, intravitreal steroids or PDT within 30 d before enrollment</td>
<td>Double-masked RCT</td>
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<td>IVR(3+PRN) 21</td>
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<td>Korea</td>
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<td>RCT</td>
<td>12</td>
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<td>NR</td>
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<td>IVB(3+PRN)+SF PDT 18</td>
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<td>Italy</td>
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<td>RCT</td>
<td>12</td>
<td>IVB(1+PRN) 45</td>
<td>65.3 ± 15</td>
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<td>IVB(1+PRN)+RF PDT 40</td>
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<td>Greece</td>
<td>Naive</td>
<td>RCT</td>
<td>12</td>
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<td>73 ± 8.5</td>
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<td>Saviano, S.</td>
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<td>Italy</td>
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<td>12</td>
<td>IVB(3+PRN) 31</td>
<td>79 ± 7.3</td>
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<td>IVB(3+PRN)+RF PDT 31</td>
<td>77 ± 7.8</td>
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<td>RCT</td>
<td>12</td>
<td>IVR(3+PRN) 16</td>
<td>81.1 ± 7.9</td>
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<td>IVR(3+PRN)+SF PDT 14</td>
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<td>77.2 ± 8.3</td>
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<td>IVB(1+PRN)+25% PDT 12</td>
<td>78.3 ± 8.6</td>
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</table>

Monotherapy, group that received anti-VEGF treatment only; PDT (SF), PDT with SF; PDT (RF), PDT with RF; IVR, intravitreal ranibizumab; IVB, intravitreal bevacizumab; PRN, as needed; NR: not recorded.

**Table 2.** Comparison of BCVA Between Monotherapy and Combination Therapy Groups at Baseline and End of the Study

<table>
<thead>
<tr>
<th>BCVA Studies, n</th>
<th>Sample Size</th>
<th>WMD</th>
<th>95% CI</th>
<th>P of χ^2</th>
<th>I^2</th>
<th>P for Overall Effect</th>
</tr>
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<tr>
<td>Baseline 7</td>
<td>Monotherapy 316 Combination 317</td>
<td>-1.612</td>
<td>-3.959 to -0.735</td>
<td>0.390</td>
<td>4.90%</td>
<td>0.178</td>
</tr>
<tr>
<td>End point 9</td>
<td>Monotherapy 405 Combination 480</td>
<td>1.928</td>
<td>-1.495 to 5.352</td>
<td>0.085</td>
<td>42.70%</td>
<td>0.270</td>
</tr>
</tbody>
</table>
Number of Anti-VEGF Treatments
Twelve studies with 363 patients in the monotherapy group and 355 patients in the combination therapy group reported the number of anti-VEGF treatments. A random-effect model was used ($P < 0.001$, $I^2 = 95.4$%), and sensitivity analysis was performed without the source of heterogeneity (Figs. 3, 4). The combination therapy group required fewer anti-VEGF treatments than the monotherapy group (WMD: 1.254; 95% CI: 0.111–2.397; $P = 0.032$).

Adverse Events Recorded at the End of the Study
Six studies reported adverse events at the end of the study. Overall, the incidence of serious adverse events (endophthalmitis, macular hole) was very low. Comparison of the number of ocular and nonocular adverse events revealed no significant difference between the two treatment groups. Table 4 shows the adverse events reported in the abovementioned six studies.

Subgroup Analyses
Subgroup analyses were only conducted for the primary outcomes such as BCVA and CRT at end of the study and the number of anti-VEGF treatments. AMD-related CNV was classified as predominantly classic, minimally classic, or occult in most selected studies, however, subgroup analysis of lesion type was not performed without enough data. Only three studies enrolled patients with previous CNV treatment (which had been at least 30 days before enrollment). Subgroup analysis of prior treatment was not performed as there was not enough data.

Verteporfin PDT Fluence
In the combination therapy group, the intervention was 50 J/cm$^2$ SF PDT and anti-VEGF treatment in seven studies and was 25 J/cm$^2$ RF PDT and anti-VEGF treatment in six studies. Subgroup analysis was performed to compare the SF PDT and RF PDT. There was no obvious trend in the effects on BCVA at the end of the study based on fluence (SD PDT: WMD: 0.947, 95% CI: –3.855 to 5.749, $P = 0.699$; RF PDT: WMD: 3.305, 95% CI: –1.130 to 18.000, $P = 0.059$, Fig. 5). The end-of-study CRT was thinner with SF PDT (WMD: 17.229; 95% CI: 5.378–29.080; $P = 0.004$), while that with RF PDT was thicker, but there was no statistical difference (WMD: –3.071; 95% CI: –11.676 to 5.534; $P = 0.484$, Fig. 6). Although the SF PDT group required fewer anti-VEGF injections, there was no significant difference (WMD: 0.230; 95% CI: –0.016 to 0.475; $P = 0.067$). However, the number of anti-VEGF treatments required was significantly reduced in the RF PDT group (WMD: 3.157; 95% CI: 1.274–5.041; $P = 0.001$, Fig. 7).

Retreatment Regimen of the Combination Therapy Group
In the combination therapy group, the retreatment regimen was PDT + anti-VEGF in seven articles and only anti-VEGF treatment in nine studies. Subgroup analysis was performed
FIGURE 3. Comparison of number of anti-VEGF treatments between the combination therapy and monotherapy groups.

FIGURE 4. Meta-analysis (random-effect model) of comparison between the two treatment groups. Sensitivity analysis was performed without the source of heterogeneity.
FIGURE 5. Comparison between end-of-study BCVA of the combination therapy subgroups (SF PDT and RF PDT) and monotherapy group.

FIGURE 6. Comparison of CRT at the end of the study between the combination therapy subgroup (SF PDT and RF PDT) and monotherapy group.
based on the retreatment regimen in the combination therapy group. No significant effects were present for the primary outcomes. The end-of-study BCVA was lower in the PDT + anti-VEGF group, but there was no significant difference (WMD: 2.345; 95% CI: -1.218 to 5.908; P = 0.197). The end-of-study CRT was thinner in the PDT + anti-VEGF group (WMD: 7.930; 95% CI: -5.514 to 21.374; P = 0.248) than in the anti-VEGF group (WMD: 1.480; 95% CI: -9.777 to 12.737; P = 0.797), but there was no significant difference. However, a reduction in the number of anti-VEGF treatments was observed in both groups without a significant difference (PDT + anti-VEGF: WMD: 2.561; 95% CI: -0.704~5.825, P = 0.124; anti-VEGF: WMD: 0.791; 95% CI: -0.045~1.618; P = 0.061).

Publication Bias

Begg’s test (P = 0.462, continuity corrected) and Egger’s test (P = 0.680) indicated that publication bias did not affect our results.

DISCUSSION

Anti-VEGF treatment targets key mediators of the angiogenic cascade, while verteporfin targets the vascular component. The different action mechanisms of anti-VEGF and verteporfin PDT on CNV provide the potential for additive or synergistic effects with combination therapy. Additionally, VEGF released after verteporfin PDT might be inhibited by antiangiogenic agents. Therefore, numerous trials have focused on whether anti-VEGF and PDT combination therapy has a better clinical outcome than anti-VEGF monotherapy. In the 12-month MONT BLANC study, Larsen et al. found that PRN (as needed) combination treatment with SF PDT and ranibizumab achieved comparable BCVA gain and anatomic improvement compared with PRN ranibizumab monotherapy, but it did not reduce the number of ranibizumab retreatments over 12 months. Krebs et al. reported that, on average, patients in the combination therapy group lost 7.1 BCVA letters, while those in the monotherapy group gained 5.1 BCVA letters. To date, which therapy regimen is superior remains controversial. The aim of the present study was to compare the efficacy and safety of anti-VEGF monotherapy versus verteporfin PDT + anti-VEGF combination treatment in nAMD.

Here, the pooled results showed no statistical difference for the baseline BCVA and CRT in the monotherapy and combination therapy groups. This suggests that the baseline condition of patients within the two groups was comparable.

As verteporfin PDT of different fluences was used in the combination therapy group, we performed subgroup analysis of SF PDT and RF PDT, the most common fluences.

Thirteen, two, and one study had a follow-up time of 12 months, 6 months, and 24 months, respectively. When the number of anti-VEGF treatments between the two treatment groups was analyzed, only the trials with 12 months’ follow-up were included. In the total analysis, the combination treatment group required fewer anti-VEGF treatments than the monotherapy group. Subgroup analysis revealed no statistical difference between the SF PDT combination treatment group and the monotherapy group. The result is comparable to that of the meta-analysis by Si et al. and other previous studies. In the meta-analysis by Tong et al., the authors analyzed only four studies from among their included trials. The use of SF PDT in these studies was categorized as combination...
## TABLE 4.
The Main Ocular and Systemic Adverse Events Reported

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Monotherapy</th>
<th>Combination</th>
<th>Sample Size</th>
<th>Incidence Rate</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular adverse event</td>
<td>4</td>
<td>5</td>
<td>266</td>
<td>0.28%</td>
<td>1.018 (0.928 - 1.116)</td>
<td>0.712</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>4</td>
<td>5</td>
<td>255</td>
<td>0.78%</td>
<td>1.014 (0.913 - 1.128)</td>
<td>0.847</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>2</td>
<td>2</td>
<td>204</td>
<td>1.0%</td>
<td>1.000 (0.540 - 1.849)</td>
<td>0.997</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>2</td>
<td>2</td>
<td>273</td>
<td>0.71%</td>
<td>1.002 (0.951 - 1.056)</td>
<td>0.857</td>
</tr>
<tr>
<td>Increased intraocular pressure</td>
<td>3</td>
<td>2</td>
<td>264</td>
<td>1.14%</td>
<td>1.008 (0.786 - 1.296)</td>
<td>0.899</td>
</tr>
<tr>
<td>Retinal pigment epithelial tear</td>
<td>2</td>
<td>2</td>
<td>212</td>
<td>0.95%</td>
<td>1.004 (0.713 - 1.442)</td>
<td>0.961</td>
</tr>
<tr>
<td>Nonocular adverse event</td>
<td>2</td>
<td>2</td>
<td>234</td>
<td>5.59%</td>
<td>1.196 (1.004 - 1.417)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

### Notes
- The end-of-study CRT of the two treatment groups was compared.
- This result is similar to that of previous meta-analyses and other published studies.
- The subgroup analysis showed no statistical difference between the end-of-study BCVA for SF PDT or RF PDT combination therapy and monotherapy.
- In the DENALI study, the mean BCVA change at month 12 was -5.3, -4.4, and -8.1 BCVA letters in the SF PDT group, RF PDT group, and ranibizumab monotherapy group, respectively.
- There was no statistical difference between both combination therapy groups and the monotherapy group.
- In the trials included in our study, the monotherapy group had a higher ratio of patients who gained ≥15 BCVA letters than the combination therapy group, but there was no statistical difference.
- The subgroup analysis of SF PDT and RF PDT yielded similar outcomes. More studies with larger sample sizes should be performed to determine the best treatment for improving BCVA.

### Treatment
- Fewer anti-VEGF treatments being required than monotherapy did not correlate to better BCVA. Further studies with larger sample sizes are needed to determine the underlying reasons.
- In combination treatment, PDT causes thrombotic occlusion in CNV, especially to mature vessels that may not be sensitive to anti-VEGF drugs due to quick pericyte enclosure. Additionally, the simultaneous anti-VEGF injection further suppresses neovascularization in CNV and inhibits VEGF release after PDT. This process may alter the CNV such that the need for anti-VEGF retreatment is delayed. In our meta-analysis, we found that RF PDT in combination treatment led to fewer anti-VEGF treatments being required than monotherapy did, while SF PDT did not. This suggests that RF verteporfin therapy improves its selectivity in nAMD, avoiding collateral physiological damage to the choroid while achieving complete CNV closure.

### References
- Saviano et al. reported that the mean number of ranibizumab treatments required was reduced in the RF verteporfin PDT combination treatment group (5.8 ± 1.3) compared with the monotherapy group (7.8 ± 1.0) (P < 0.0001).
- In the study by Semeraro et al., the mean number of ranibizumab treatments required was reduced in the RF verteporfin PDT combination treatment group (5.8 ± 1.3) compared with the monotherapy group (7.8 ± 1.0) (P < 0.0001).
- Tan et al. included only ranibizumab as anti-VEGF treatment in seven studies. In the analysis by Tong et al., of eight studies, the subgroup analysis of the study by Kaiser et al.
et al. increased the statistical error. Moreover, the number of anti-VEGF treatments was analyzed in only four studies of the eight trials included, and these studies categorized SF PDT as combination treatment. In our study, 16 RCTs of moderate to high quality were included, and subgroup analyses of different-fluence PDT and different retreatment regimens in the combination therapy group were performed. Our meta-analysis is, to our knowledge, the first subgroup analysis of different-fluence PDT combination treatment versus monotherapy.

Ranibizumab is a recombinant humanized monoclonal antibody fragment of 48 kDa produced in Escherichia coli. It is formed by a human immunoglobulin G1 (IgG1) light chain linked by a disulfide bond to a human IgG1 Fab heavy chain, with murine anti-VEGF-A complementary determining regions.53 Ranibizumab binds with high affinity to VEGF-A isoforms, mainly to VEGF165.24 Aflibercept is a recombinant fusion protein of 96.9 kDa produced in Chinese hamster ovary cells, which contains around 15% glycosylation, giving it a final molecular weight of 115 kDa. It is a chimeric protein that contains the second Ig domain of human VEGF receptor-1 (VEGFR-1) fused with the third Ig domain of human VEGFR-2, both of which are in turn fused to the constant region of human IgG1. Aflibercept binds to all VEGF-A isoforms as well as other isoforms of the VEGF family (VEGF-B, C, and D), and also to placental growth factor.54 A very recent study has brought to light a similar binding affinity of ranibizumab and aflibercept to VEGF165.56 Fixed-dose bimonthly aflibercept injections have been reported to have efficacy comparable to that of monthly ranibizumab injections.57 However, in our study, no RCTs comparing aflibercept and PDT combination therapy with aflibercept monotherapy on neovascular AMD were retrieved. More clinical trials concerning aflibercept and PDT in neovascular AMD are needed in the future.

There are limitations to this study. AMD-related CNV was classified as predominantly classic, minimally classic, or occult in most selected studies; however, subgroup analysis of lesion type was not performed because there was not enough data. Only three studies enrolled patients with previous CNV treatment,18,22,24 and the treatment was at least 30 days before enrollment. Lim et al.22 found that naive eyes showed better improvements in BCVA and CTR than did previously PDT-treated eyes. The total number of bevacizumab injections was not reduced when PDT was given, either among all patients or in a subgroup of naive patients. Subgroup analysis of prior treatment was not performed because there was not enough data.

In conclusion, combination therapy with verteporfin PDT and anti-VEGF therapy is effective for achieving BCVA gain and CRT reduction compared with anti-VEGF monotherapy. Combination therapy with RF PDT has the potential to decrease the number of anti-VEGF injections, thereby reducing the overall treatment burden and serious adverse events associated with intravitreal injection. However, monotherapy is associated with a higher ratio of patients who gain ≥15 BCVA letters than does combination therapy, despite the lack of statistical difference. Further research with a larger sample size is needed to determine the best treatment for maximally improving BCVA.

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