E.6.3 Adjunctive therapies

RQ13: What is the effectiveness of adjunctive therapies for the treatment of late AMD (wet active)?

Bibliographic reference	**Ahmadieh H, Taei R, Riazi-Esfahani M, Piri N, Homayouni M, Daftarian N, and Yaseri M. 2011. "Intravitreal bevacizumab versus combined intravitreal bevacizumab and triamcinolone for neovascular age-related macular degeneration: six-month results of a randomized clinical trial". Retina 31:1819-26.**
Country/ies where the study carried out	University of Tehran, Iran
Study type	RCT
Aim of the study	To determine whether combined intravitreal bevacizumab (IVB) and triamcinolone (IVT) is more effective than IVB alone in neovascular age-related macular degeneration
Study dates	Not reported
Sources of funding	Not reported
Sample size	120

Bibliographic reference	**Ahmadieh H, Taei R, Riazi-Esfahani M, Piri N, Homayouni M, Daftarian N, and Yaseri M. 2011. "Intravitreal bevacizumab versus combined intravitreal bevacizumab and triamcinolone for neovascular age-related macular degeneration: six-month results of a randomized clinical trial". Retina 31:1819-26.**
Inclusion Criteria	Patients with subfoveal choroidal neovascularisation, including predominantly classic, minimally classic, occult, and retinal angiomatous proliferation secondary to age-related macular degeneration.
Exclusion Criteria	Patients' eye were presence of diabetic retinopathy, glaucoma, or any other type of macular disease; Patients eye had previous history of treatment (other than photodynamic therapy)
Baseline characteristics	

	Combined intravitreal bevacizumab with intravitreal triamcinolone (IVB/IVT)	Intravitreal bevacizumab (IVB)	P
Number eyes	55	60	
Mean age (SD)	71(8)	71 (8)	0.885
Gender (F/M)	34/21	35/25	0.703
Smoking (%)	15 (27)	13 (22)	0.484
CNV type (%)			0.971
Minimally classic	10 (18)	12 (20)	
Dominantly classic	20 (36)	22 (37)	
Occult	15 (27)	17 (28)	
RAP	10 (18)	9 (15)	
PED	3 (6)	3 (5)	>0.999
CNV size (%)			0.084
<2	17 (31)	18 (30)	
2-4	29 (53)	22 (37)	
>4	9 (16)	20 (33)	
BCVA ETDRS (SD)	33 (18)	37 (21)	0.351

Bibliographic reference	**Ahmadieh H, Taei R, Riazi-Esfahani M, Piri N, Homayouni M, Daftarian N, and Yaseri M. 2011. "Intravitreal bevacizumab versus combined intravitreal bevacizumab and triamcinolone for neovascular age-related macular degeneration: six-month results of a randomized clinical trial". Retina 31:1819-26.**
	CMT µm (SD) | 353 (119) | 341 (158) | 0.716
Study visits and procedures	Patients underwent a baseline evaluation; Patients were assigned randomly to IVB or IVB/IVT groups Patients in the IVB group received mandated therapy with 3 consecutive intravitreal injection of 1.25mg/0.05ml of bevacizumab with 6 weeks apart; Patients in the IVB/IVT group, intravitreal injection of 2mg/0.05mL of triamcinolone acetonide was added to bevacizumab in the first session. The second and third injections consisted of bevacizumab only; Clinical examinations and optical coherence tomography were repeated at 6-week intervals. Fluorescein angiography was repeated 6 weeks and 24 weeks after the first injection. A fourth IVB injection was given eyes with active CNV at Week 24 according to clinical findings. Intravitreal triamcinolone injection was not repeated during the follow-up period
Intervention	Combined intravitreal bevacizumab with intravitreal triamcinolone (IVT)
Comparator	Intravitreal bevacizumab (IVB)
Outcomes	Primary outcome: Change in best-corrected visual acuity Secondary outcome: Central macular thickness Need for a fourth injection Adverse events
Analyses	Chi-square, Fisher exact test and Mann-Whitney test T-test Marginal regression based on generalised estimating equation
Length of follow up	24 weeks (6 months)
Results	| Combined intravitreal bevacizumab with intravitreal | Intravitreal bevacizumab (IVB) | Effect (95%CI) | P value

Bibliographic reference	Ahmadieh H, Taei R, Riazi-Esfahani M, Piri N, Homayouni M, Daftarian N, and Yaseri M. 2011. "Intravitreal bevacizumab versus combined intravitreal bevacizumab and triamcinolone for neovascular age-related macular degeneration: six-month results of a randomized clinical trial". Retina 31:1819-26.

	triamcinolone (IVB/IVT)			
No. of eyes that needed for retreatment at Week 24 (%)	19 (34.5)	32 eyes (53.3)	0.65 (0.42, 1.00)	0.04
Best-corrected visual acuity changes (ETDRS letter score)				
0-6 weeks	8.5 (14.4)	3.8 (8.9)	4.7 (0.2, 9.0)	0.04
0-12 weeks	11.8(16.6)	6.2 (10.8)	5.6 (0.5, 10.8)	0.03
0-18 weeks	12.9 (15.6)	8.4 (13.6)	4.5 (-1.1, 10.0)	0.11
0-24 weeks	11.3 (17.2)	8.7 (15.6)	2.6 (-3.5, 8.7)	0.40
CMT changes				
0-6 weeks	-79.6 (124.9)	-58.8 (131.3)	-20.8 (-73.6, 32.0)	0.43
0-12 weeks	-89.7 (154.9)	-85.3 (128.5)	-4.4 (-63.4, 54.6)	0.88
0-18 weeks	-114.1 (151.7)	-96.3 (156.6)	17.8 (-82.0, 46.4)	0.58
0-24 weeks	-89.1 (162.5)	-88.4 (117.1)	0.7 (-59.4, 58.0)	0.98

No systemic AE reported.

Missing data handling/loss to follow up	115 eyes of 115 patients completed 6 months follow-up.
Was allocation adequately concealed?	Groups of participants were blinded to the optometrist who conducted visual acuity assessment.
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear

Bibliographic reference	Ahmadieh H, Taei R, Riazi-Esfahani M, Piri N, Homayouni M, Daftarian N, and Yaseri M. 2011. "Intravitreal bevacizumab versus combined intravitreal bevacizumab and triamcinolone for neovascular age-related macular degeneration: six-month results of a randomized clinical trial". Retina 31:1819-26.
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	Yes
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Bashshur Z F, Schakal A R, El-Mollayess G M, Arafat S, Jaafar D, and Salti H I. 2011. "Ranibizumab monotherapy versus single-session verteporfin photodynamic therapy combined with as-needed ranibizumab treatment for the management of neovascular age-related macular degeneration". Retina (Philadelphia, and Pa.) 31:636-44.
Coutry/ies where the study carried out	Beirut, Lebanon
Study type	Open label RCT
Aim of the study	To compare verteporfin photodynamic therapy combined with intravitreal ranibizumab (combination therapy) versus ranibizumab monotherapy for management of neovascular age-related macular degeneration.
Study dates	June 2007 and January 2008
Sources of funding	Novartis
Sample size	30 patients (40 eyes)
Inclusion Criteria	Age 50 years or older Subfoveal CNV secondary to AMD as determinately by fluorescein angiography Presence of fluid in the macular on OCT

Bibliographic reference	**Bashshur Z F, Schakal A R, El-Mollayess G M, Arafat S, Jaafar D, and Salti H I. 2011. "Ranibizumab monotherapy versus single-session verteporfin photodynamic therapy combined with as-needed ranibizumab treatment for the management of neovascular age-related macular degeneration". Retina (Philadelphia, and Pa.) 31:636-44.**
	CNV≤5,400µm in greatest linear dimension BCVA, using ETDRS charts, of 20/50 to 20/400 in the study eye Area of CNV at least 50% of total lesion area
Exclusion Criteria	Corneal, lenticular or vitreous opacification that prevents good quality angiograms on OCT History of uveitis Other ocular conditions that may affect vision Subfoveal scarring or haemorrhage Previous treatment for CNV Anti-VEGF treatment less than 3 months before enrolment and or Verteporfin PDT less than 6 months before enrolment
Baseline characteristics	

	Combination Therapy	Monotherapy	P values
Number of patients	13	17	-
Number of eyes	20	20	-
Mean age (SD)	71.0 (8.0)	75.6 (6.3)	0.19
Number of male	9	9	
CNV type			
Occult	7	9	0.49
Minimally classic	8	6	0.58
Predominantly classic	5	5	0.84
Previous treatment			
None	9	10	0.71
Anti-VEGF	9	8	0.55
PDT	2	2	0.71

<table>
<tr><th>Bibliographic reference</th><th>Bashshur Z F, Schakal A R, El-Mollayess G M, Arafat S, Jaafar D, and Salti H I. 2011. "Ranibizumab monotherapy versus single-session verteporfin photodynamic therapy combined with as-needed ranibizumab treatment for the management of neovascular age-related macular degeneration". Retina (Philadelphia, and Pa.) 31:636-44.</th></tr>
<tr><td>Study procedures</td><td>Patients were allocated to ranibizumab monotherapy or verteporfin PDT in combination with intravitreal ranibizumab in a 1:1 ratio;
Patients allocated to the monotherapy group received intravitreal ranibizumab (0.5mg);
Patients assigned to the combination therapy group were treated with PDT with verteporfin, within an hour of PDT, an intravitreal injection of ranibizumab was administrated to the treated eye;
The treatment in both groups was divided into an induction phase and a follow-up phase. The introduction phase of the monotherapy group consisted of the initial ranibizumab injection followed by 2 consecutive monthly injections for a total of 3 injections. The induction phase on the combination therapy group consisted of the primary PDT session followed by the ranibizumab injection; however, no additional obligation consecutive injections were given. After the initial treatment, patients were seen at 1 week and then followed monthly.</td></tr>
<tr><td>Intervention</td><td>Combined therapy: patients were treated with PDT with verteporfin, within an hour of PDT, an intravitreal injection of ranibizumab was administrated to the treated eye.</td></tr>
<tr><td>Comparator</td><td>Monotherapy ranibizumab</td></tr>
<tr><td>Outcomes</td><td>A proportion of patients who lost < 15 letter in BCVA score at 12 months compared with baseline
Mean change in BCVA score
The proportion of patients who gain ≥15 letters in BCVA
The proportion of patients with Snellen equivalent visual acuity of 20/200 or worse compared with baseline
The effect of combination therapy vs monotherapy on the size of CNV
The effect of both treatment on the CRT
The number of intravitreal ranibizumab injections over 12 months in 2 groups</td></tr>
<tr><td>Analyses</td><td>Generalised estimation equation</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>Combined therapy (PDT + ranibizumab) (n=20 eyes)</th><th>Intravitreal ranibizumab (n=20 eyes)</th><th>Effect (95%CI)</th><th>P values</th></tr>
<tr><td>Injection in 12 months</td><td></td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Bashshur Z F, Schakal A R, El-Mollayess G M, Arafat S, Jaafar D, and Salti H I. 2011. "Ranibizumab monotherapy versus single-session verteporfin photodynamic therapy combined with as-needed ranibizumab treatment for the management of neovascular age-related macular degeneration". Retina (Philadelphia, and Pa.) 31:636-44.

Introduction phase				
Total number	60	119	-59	
Median (range)	3 (1 to 6)	6 (3 to 10)	-3	<0.001
Follow-up phase				
Median (range)	2 (0 to 5)	3 (0 to 6)	-1	0.13
% of patients not require injection after introduction phase	20%	15%	1.33 (0.34, 5.21)	1.0
Best-corrected visual acuity changes				
Baseline (SE)	53.4 (3.2)	53.8 (2.6)	-0.4 (-8.5, 7.7)	0.88
After 12 months	56.6 (3.3)	65.8 (2.5)	-9.2 (-17.4, -1.2)	
Letter gain by 12 months	3.2	12.0	-8.8	-
% change by 12 month	0.07 (0.04)	0.32 (0.13)	-0.25	0.03
Central macular thickness changes				
Baseline (SE)	292.5 (18.1)	283.0 (16.0)	9.5 (-37.9, 56.9)	0.52
After 12 months	219.9 (15.0)	212.3 (11.2)	7.6 (-29.1, 44.3)	0.62
Decrease by 12 months	72.6	70.7	1.9	-
% change by 12 month	-0.22 (0.04)	-0.19 (0.07)	-0.03	0.71

Bibliographic reference	Bashshur Z F, Schakal A R, El-Mollayess G M, Arafat S, Jaafar D, and Salti H I. 2011. "Ranibizumab monotherapy versus single-session verteporfin photodynamic therapy combined with as-needed ranibizumab treatment for the management of neovascular age-related macular degeneration". Retina (Philadelphia, and Pa.) 31:636-44.
	Safety: macular oedema (8); retinal pigment epithelium tear (1): Cataract by Month 10 (1); 4.00 (0.97, 16.55)
Missing data handling/loss to follow up	All patients completed the 12 month period of the study
Was allocation adequately concealed?	No (open-label), but no detail described in the study
Was knowledge of the allocated intervention adequately prevented during the study?	No
Was the allocation sequence adequately generated?	Unclear (not reported)
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size (20 eyes in each group)
Were incomplete outcome data adequately addressed?	All completed follow-up
Are reports of the study free of suggestion of selective outcome reporting?	Yes

<table>
<tr><th>Bibliographic reference</th><th>Datseris I, Kontadakis G A, Diamanti R, Datseris I, Pallikaris I G, Theodossiadis P, and Tsilimbaris M K. 2015. "Prospective comparison of low-fluence photodynamic therapy combined with intravitreal bevacizumab versus bevacizumab monotherapy for choroidal neovascularization in age-related macular degeneration". Seminars in Ophthalmology 30:112-7.</th></tr>
<tr><td>Coutry/ies where the study carried out</td><td>Greece</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Aim of the study</td><td>To evaluate combination treatment with reduced-fluence photodynamic therapy (RDPDT) with verteporfin and intravitreal bevacizumab, compared to bevacizumab alone, for choroidal neovascularization (CNV) in age-related macular degeneration</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Sources of funding</td><td>Not reported</td></tr>
<tr><td>Sample size</td><td>100</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients with predominantly classic and occult CNV due to AMD in one or both eyes;
All eye were treatment naive
Leakage documented by fluorescein angiography, intraretinal or subretinal fluid in optical coherence tomography
Largest linear dimension of the lesion equal to four disk areas
Corrected distance visual acuity of 20/400 or more</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients with other ocular pathologies within 2 months prior to initial assessment were excluded;
Patients’ fluorescein angiography and OCT images were of inadequate quality due to significant optical media opacities;
Patients would presumably need ophthalmic surgery within the following year;</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Combined therapy (PCT + bevacizumab)</th><th>Intravitreal bevacizumab</th><th>P values</th></tr>
<tr><td>Number of patients</td><td>49</td><td>46</td><td></td></tr>
<tr><td>Male (%)</td><td>13 (27)</td><td>16 (35)</td><td></td></tr>
<tr><td>Mean age (SD)</td><td>73 (8.5)</td><td>74 (10.3)</td><td>0.543</td></tr>
<tr><td>CDVA (logMAR)</td><td>0.74 (0.32)</td><td>0.71 (0.32)</td><td>0.691</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="2">Datseris I, Kontadakis G A, Diamanti R, Datseris I, Pallikaris I G, Theodossiadis P, and Tsilimbaris M K. 2015. "Prospective comparison of low-fluence photodynamic therapy combined with intravitreal bevacizumab versus bevacizumab monotherapy for choroidal neovascularization in age-related macular degeneration". Seminars in Ophthalmology 30:112-7.</td></tr>
<tr><td></td><td colspan="2"><table>
<tr><td>CFT</td><td>460.73 (110.68)</td><td>441.11 (122.59)</td><td>0.414</td></tr>
</table></td></tr>
<tr><td>Study procedures</td><td colspan="2">All patients underwent a complete ophthalmic examination before treatment;
Patients were allocated to the group with bevacizumab monotherapy were administrated intravitreal injection (1.25mg);
Patients allocated in the combination treatment group underwent one session of low-fluence PDT with verteportin, one hour later, intravitreal injection of bevacizumab (1.25mg);
Patients were assessed in a monthly basis and intravitreal bevacizumab was re-administrated at each visit if at least one of the following functional and anatomic criteria was fulfilled: a≥100μm increase in CFT; decrease in CDVA of>5 letters; presence of subretinal fluid and/or intraretinal in OCT; and presence of new haemorrhage in biomicroscopy
Data were collected 1,3,6,9 and 12 months after initiation of treatment.</td></tr>
<tr><td>Intervention</td><td colspan="2">Combined therapy: PCT + bevacizumab</td></tr>
<tr><td>Comparator</td><td colspan="2">Bevacizumab monotherapy</td></tr>
<tr><td>Outcomes</td><td colspan="2">Number of reinjections at the end of follow-up
CDVA (corrected-distance visual acuity)
CFT</td></tr>
<tr><td>Analyses</td><td colspan="2">Independent samples t-test
Chi-square test</td></tr>
<tr><td>Length of follow up</td><td colspan="2">12 months</td></tr>
<tr><td>Results</td><td colspan="2"><table>
<tr><th></th><th>Combined therapy (PCT + bevacizumab) (n=49)</th><th>Intravitreal bevacizumab (n=46)</th><th>Effect (95%CI)</th><th>P value</th></tr>
<tr><td>Reinjections</td><td>4.45 (0.15)</td><td>6.96 (0.29)</td><td>-2.51
(-3.15, -1.87)</td><td><0.001</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Datseris I, Kontadakis G A, Diamanti R, Datseris I, Pallikaris I G, Theodossiadis P, and Tsilimbaris M K. 2015. "Prospective comparison of low-fluence photodynamic therapy combined with intravitreal bevacizumab versus bevacizumab monotherapy for choroidal neovascularization in age-related macular degeneration". Seminars in Ophthalmology 30:112-7.				
	Corrected distance visual acuity (logMAR)	0.57 (0.04)	0.54 (0.04)	0.03 (-0.08, 0.14)	0.584
	Gain in letters	8.37 (1.77)	8.64 (2.11)	-0.27 (-5.65, 5.11)	0.922
	No. of patients (%) had a stable or improved vision (loss of <15 letters)	44 (89.9)	43 (93.5)	0.96 (0.85, 1.08)	
	No. of patients (%) gained 15 or more letter	21 (42.8)	20 (43.5)	0.99 (0.62, 1.56)	
	CFT, µm				
	Baseline (SE)	460.73 (15.81)	441.11(18.08)	19.62 (-58.93, 98.17)	
	Month 12 (SE)	290.84 (13.75)	286.00 (8.55)	4.84 (-27.37, 37.05)	0.768
Missing data handling/loss to follow up	Not reported (based on results, 5 patients did not complete the 12 month follow up)				
Was allocation adequately concealed?	Unclear				
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear				
Was the allocation sequence adequately generated?	Yes				

Bibliographic reference	Datseris I, Kontadakis G A, Diamanti R, Datseris I, Pallikaris I G, Theodossiadis P, and Tsilimbaris M K. 2015. "Prospective comparison of low-fluence photodynamic therapy combined with intravitreal bevacizumab versus bevacizumab monotherapy for choroidal neovascularization in age-related macular degeneration". Seminars in Ophthalmology 30:112-7.
Was the study apparently free of other problems that could put it at a high risk of bias?	Unclear
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, Iwata E, Maruko R, Iida T, Shiraga F, Yuzawa M, Terasaki H, Ishibashi T, Shiragami C, Shirakata Y, Hara C, Sawa M, and Takahashi K. 2015. "Initial Versus Delayed Photodynamic Therapy in Combination with Ranibizumab for Treatment of Polypoidal Choroidal Vasculopathy". Retina (Philadelphia, and Pa.) 35:1569-76.
Coutry/ies where the study carried out	Japan
Study type	RCT
Aim of the study	To compare the 1-year results of initial or deferred photodynamic therapy (PDT) combined with intravitreal ranibizumab (IVR) for eyes with polypoidal choroidal vasculopathy.
Study dates	January 10 2011 to October 5 2012
Sources of funding	Not reported
Sample size	72 patients (72 eyes)
Inclusion Criteria	Male patients were older than 50 years with treatment-naive PCV who met the following criteria: BCVA ranged from 01. To 0.7 using a Landolt chart The greatest lesion size was less than 12 macular photocoagulation study disk areas

<table>
<tr><th>Bibliographic reference</th><td>Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, Iwata E, Maruko R, Iida T, Shiraga F, Yuzawa M, Terasaki H, Ishibashi T, Shiragami C, Shirakata Y, Hara C, Sawa M, and Takahashi K. 2015. "Initial Versus Delayed Photodynamic Therapy in Combination with Ranibizumab for Treatment of Polypoidal Choroidal Vasculopathy". Retina (Philadelphia, and Pa.) 35:1569-76.</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients' eyes had central serous chorioretinopathy, retinal vascular disease, any neovascular maculopathy, glaucoma, or a history of intraocular surgery after phacoemulsification.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Intravitreal ranibizumab</th><th>Combined therapy (PCT + ranibizumab)</th></tr>
<tr><td>Number of eyes</td><td>35</td><td>37</td></tr>
<tr><td>Mean age (SD)</td><td>73.8 (7.1)</td><td>73.6 (5.8)</td></tr>
<tr><td>Visual acuity (logMAR)</td><td>0.51 (0.24)</td><td>0.50 (0.24)</td></tr>
<tr><td>Visual acuity (ETDRS)</td><td>54.9 (13.1)</td><td>54.3 (17.9)</td></tr>
<tr><td>Central macular thickness</td><td>345.6 (118.6)</td><td>360.5 (174.4)</td></tr>
<tr><td>Bilatelal PCV (%)</td><td>5 (14.3)</td><td>7 (18.9)</td></tr>
<tr><td>Subfoveal polys (%)</td><td>19 (54.3)</td><td>16 (43.2)</td></tr>
<tr><td>Multiple polys (%)</td><td>24 (68.6)</td><td>2 (56.8)</td></tr>
<tr><td>Subretinal haemorrhage</td><td>10 (28.6)</td><td>13 (35.1)</td></tr>
<tr><td>Pigment epithelial detachment eyes (%)</td><td>10 (28.6)</td><td>12 (32.4)</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were randomised to verteporfin PDT plus intravitreal ranibizumab (IVR) combination therapy or ranibizumab alone in a 1:1 ratio;
In combination therapy group, PDT was administered within 1 week after IVR injection;
In both groups, IVR was administered once for 3 consecutive months</td></tr>
<tr><td>Intervention</td><td>Ranibizumab +PDT</td></tr>
<tr><td>Comparator</td><td>Ranibizumab monotherapy</td></tr>
<tr><td>Outcomes</td><td>Differences in the changes in BCVA at 12 months from baseline between 2 groups</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="5">Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, Iwata E, Maruko R, Iida T, Shiraga F, Yuzawa M, Terasaki H, Ishibashi T, Shiragami C, Shirakata Y, Hara C, Sawa M, and Takahashi K. 2015. "Initial Versus Delayed Photodynamic Therapy in Combination with Ranibizumab for Treatment of Polypoidal Choroidal Vasculopathy". Retina (Philadelphia, and Pa.) 35:1569-76.</td></tr>
<tr><td>Length of follow up</td><td colspan="5">12 months</td></tr>
<tr><td>Results</td><td colspan="5">
<table>
<tr><td></td><td>Intravitreal ranibizumab</td><td>Combined therapy (ranibizumab +PDT)</td><td>Effect (95%CI)</td><td>P values</td></tr>
<tr><td>Number of eyes</td><td>31</td><td>29</td><td></td><td></td></tr>
<tr><td>BCVA logMAR</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Baseline (SD)</td><td>0.50 (0.24)</td><td>0.52 (0.25)</td><td>0.02 (-0.10, 0.14)</td><td></td></tr>
<tr><td>Month 12 (SD)</td><td>0.30 (0.27)</td><td>0.29 (0.27)</td><td>-0.01 (-0.11, 0.13)</td><td></td></tr>
<tr><td>N (%) of patients had improved VA≥15 letters</td><td>15 (48.4)</td><td>13 (44.8)</td><td>0.93 (0.54, 1.60)</td><td></td></tr>
<tr><td>CRT</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Baseline (SD)</td><td>343.6 (108.6)</td><td>360.5 (174.4)</td><td>16.9 (-57.2, 91.0)</td><td>0.63</td></tr>
<tr><td>Month 12</td><td>206.0 (67.3)</td><td>187.2 (87.5)</td><td>-18.8 (-58.5, 20.9)</td><td>0.68</td></tr>
<tr><td>Additional treatment</td><td></td><td></td><td></td><td></td></tr>
<tr><td>No. of patients without additional treatment</td><td>6</td><td>19</td><td>3.39 (1.57, 7.28)</td><td></td></tr>
<tr><td>Mean additional IVRs (Month 3 to 12)</td><td>3.8 (2.3)</td><td>1.5 (1.8)</td><td>-2.3 (-3.3, -1.3)</td><td><0.001</td></tr>
<tr><td>Mean additional PDTs</td><td>0.48 (0.56)</td><td>0.14 (0.35)</td><td>-0.35 (-0.6, -0.1)</td><td>0.0134</td></tr>
<tr><td>Treatment-emergent AEs</td><td>2*</td><td>0</td><td></td><td></td></tr>
</table>
*1 patients in the combined therapy group had myocardial infarction 11 days after ranibizumab injection; 1 eyes in the combined therapy group developed a new subretinal haemorrhage smaller than 3 disk areas at Month 5, which resolved spontaneously and did not affect the BCVA
</td></tr>
</table>

Bibliographic reference	Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, Iwata E, Maruko R, Iida T, Shiraga F, Yuzawa M, Terasaki H, Ishibashi T, Shiragami C, Shirakata Y, Hara C, Sawa M, and Takahashi K. 2015. "Initial Versus Delayed Photodynamic Therapy in Combination with Ranibizumab for Treatment of Polypoidal Choroidal Vasculopathy". Retina (Philadelphia, and Pa.) 35:1569-76.
Missing data handling/loss to follow up	During the study, 8 patients in the combined therapy and 4 in monotherapy group withdrew from the study.
Was allocation adequately concealed?	No (open treatment allocation)
Was knowledge of the allocated intervention adequately prevented during the study?	No
Was the allocation sequence adequately generated?	Stratified based on BCVA
Was the study apparently free of other problems that could put it at a high risk of bias?	Only males were included in the study
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Hatz K, Schneider U, Henrich P B, Braun B, Sacu S, and Prunte C. 2015. "Ranibizumab plus verteporfin photodynamic therapy in neovascular age-related macular degeneration: 12 months of retreatment and vision outcomes from a randomized study". Ophthalmologica 233:66-73.
Coutry/ies where the study carried out	USA
Study type	Double blinded RCT
Aim of the study	To investigate the injection frequency and visual acuity (VA) outcomes with combination therapy (ranibizumab plus verteporfin photodynamic therapy, PDT) versus monotherapy (ranibizumab).

Bibliographic reference	**Hatz K, Schneider U, Henrich P B, Braun B, Sacu S, and Prunte C. 2015. "Ranibizumab plus verteporfin photodynamic therapy in neovascular age-related macular degeneration: 12 months of retreatment and vision outcomes from a randomized study". Ophthalmologica 233:66-73.**
Study dates	Not reported
Sources of funding	Novartis Pharma AG
Sample size	40
Inclusion Criteria	Patients aged ≥50 years with subfoveal CNV secondary to AMD; Patients had a VA letter score of 73-24 on an ETDS chart Patients had a lesion that consisted of≥50% active CNV as shown by fluorescein angiography
Exclusion Criteria	Laser photocoagulation, intravitreal steroids or verteporfin PDT in the study eye within 30 days before enrolment; Prior external-beam radiation therapy, vitrectomy or transpupillary thermotherapy; A history of surgery in the study eye within the past 2 months Participation in any studies of investigational drugs within the past month; Any trials of antiangiogenic drugs A history of intravitreal anti VEGF treatment
Baseline characteristics	

	Combination therapy	Monotherapy
Number of patients	19	21
Number of female (%)	13 (68.4)	14 (66.7)
Mean age, years	79	78
Mean VA letter score (ETDRS)	52.1	52.1
Patients with prior PDT	7 (36.8)	4 (19.0)
CNV types		
Occult without classic	15 (78.9)	10 (47.6)
Minimally classic	1 (5.3)	4 (19.0)
Predominantly classic	3 (15.8)	7 (33.3)
Mean CRT (SD),µm	294 (70)	324 (98)
Mean total area of lesion, mm2	8.2 (3.6)	9.4 (7.70

<table>
<tr><th>Bibliographic reference</th><th>Hatz K, Schneider U, Henrich P B, Braun B, Sacu S, and Prunte C. 2015. "Ranibizumab plus verteporfin photodynamic therapy in neovascular age-related macular degeneration: 12 months of retreatment and vision outcomes from a randomized study". Ophthalmologica 233:66-73.</th></tr>
<tr><td>Study procedures</td><td>Patients were randomised 1:1 to combination therapy or monotherapy;
Patients received standard-fluence verteportin PDT or sham PDT at baseline and intravitreal injection with ranibizumab (0.3mg) within 1 hour after PDT in the study eye, followed by 2 further ranibizumab (0.3mg) injections at monthly interval;
Patients were followed up at 30-day intervals throughout the study
At the follow-up visit at month 3-11, ranibizumab injections were administered if there was a decrease in BCVA of>5 letter compared with the highest previous BCVA values or if there was an increase in CRT on OCT≥100µm compared with the lowest previous value;
The minimum interval between ranibizumab treatment was 28 days</td></tr>
<tr><td>Intervention</td><td>Combination therapy: ranibizumab plus single standard-fluence verteporfin PDT</td></tr>
<tr><td>Comparator</td><td>Monotherapy ranibizumab plus a single sham PDT</td></tr>
<tr><td>Outcomes</td><td>Best corrected visual acuity; central macular thickness</td></tr>
<tr><td>Analyses</td><td>Pearson chi square
Bonferroni-Holm stepdown test</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>Combined therapy (ranibizumab +PDT)</th><th>Intravitreal ranibizumab</th><th>Effect (95%CI)</th></tr>
<tr><td>Number of patients</td><td>19</td><td>21</td><td></td></tr>
<tr><td>Re-treatment</td><td></td><td></td><td></td></tr>
<tr><td>Total number, Month 3-12</td><td>23</td><td>53</td><td></td></tr>
<tr><td>% of patients had no retreatment, Month12</td><td>47%</td><td>23%</td><td>1.99 (0.81, 4.89)</td></tr>
<tr><td>BCVA, Mean improvement (letters) from baseline</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Hatz K, Schneider U, Henrich P B, Braun B, Sacu S, and Prunte C. 2015. "Ranibizumab plus verteporfin photodynamic therapy in neovascular age-related macular degeneration: 12 months of retreatment and vision outcomes from a randomized study". Ophthalmologica 233:66-73.
	Month 6 (SD) 8.5 (2.5) 10.2 (1.8) -1.70 (-3.1, -0.3) Month 12 (SD) 9.0 (2.8) 7.5 (2.9) 1.5 (-0.3, 3.3) % of patients gained ≥15 letters Month 6 22.2% (n=4) 31.6% (n=7) 0.63 (0.22, 1.82) Month 12 33.3% (n=6) 36.8% (n=8) 0.83 (0.35, 1.95) CRT change from baseline,µm Month 12 -89 (24) -101 (25) -12 (-27.2, 3.2) Adverse events No. of patients (%) 10 (52.6) 11 (52.4) 1.00 (0.56, 1.81)
Missing data handling/loss to follow up	3 patients discontinued after the initial 3 loading injection of ranibizumab (2 in monotherapy and 1 in the combination therapy group) 1 patient discontinued due to an allergy 2 were unwilling to attend monthly follow-up
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size Variation in patients' baseline characteristics (more people in combined group previously received PDT, and more patients with occult without classic CNV in the combined group)

Bibliographic reference	Hatz K, Schneider U, Henrich P B, Braun B, Sacu S, and Prunte C. 2015. "Ranibizumab plus verteporfin photodynamic therapy in neovascular age-related macular degeneration: 12 months of retreatment and vision outcomes from a randomized study". Ophthalmologica 233:66-73.
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Kaiser P K, Boyer D S, Cruess A F, Slakter J S, Pilz S, Weisberger A, and Group Denali Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study". Ophthalmology 119:1001-10.
Coutry/ies where the study carried	USA
Study type	Double-blinded RCT
Aim of the study	To demonstrate non-inferiority of ranibizumab in combination with verteporfin photodynamic therapy (PDT) versus ranibizumab monotherapy in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration (AMD).
Study dates	Not reported
Sources of funding	Novartis Pharma AG
Sample size	321
Inclusion Criteria	Patients were 50 years of age or older and had subfoveal CNV secondary to neovascular AMD BCVA letter score in the study eye between 73 and 24 letters Maximum permitted linear dimension of the total lesion was 5400µm Total CNV area encompassed within the lesion had to be more than 50% of the total lesion area
Exclusion Criteria	Patients received prior treatment for neovascular AMD in the study eye Patients had uncontrolled glaucoma, angioid streaks, presumed ocular histoplasmosis syndrome, pathological myopia or CNV secondary to cause other than neovascular AMD

<table>
<tr><th>Bibliographic reference</th><td>Kaiser P K, Boyer D S, Cruess A F, Slakter J S, Pilz S, Weisberger A, and Group Denali Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study". Ophthalmology 119:1001-10.</td></tr>
<tr><td></td><td>Patients had presence of fibrosis, haemorrhage, pigment epithelial detachments, or other hypofluorescent lesion obscuring more than 50% of the CNV lesion
Patients had presence of retinal pigment epithelial tear.</td></tr>
<tr><td>Baseline characteristics</td><td><table>
<tr><td></td><td>SF verteportin +ranibizumab</td><td>RF verteportin +ranibizumab</td><td>Sham verteportin +ranibizumab</td></tr>
<tr><td>Number of patients</td><td>104</td><td>105</td><td>112</td></tr>
<tr><td>Mean BCVA score, letters</td><td>53.8</td><td>54.6</td><td>54.5</td></tr>
</table></td></tr>
<tr><td>Study procedures</td><td>Patients were randomised 1:1:1 for receiving stand fluence verteporfin plus intravitreal ranibizumab (combination therapy), reduce fluence verteporfin plus intravitreal ranibizumab (combination therapy) or sham verteporfin plus intravitreal ranibizumab
Patients in the verteporfin PDT combination therapy groups received PDT on day 1 and PRN for months 3 through 11 within a minimum treatment interval of 90 days
Ranibizumab (0.5mg) was administrated at baseline and month 1 and 2, followed by PRN at a 30 day interval for months 3 through 11.</td></tr>
<tr><td>Intervention</td><td>Patients were randomised 1:1:1 for receiving standard fluence verteporfin plus intravitreal ranibizumab (combination therapy), reduce fluence verteporfin plus intravitreal ranibizumab (combination therapy)</td></tr>
<tr><td>Comparator</td><td>Sham verteporfin plus intravitreal ranibizumab</td></tr>
<tr><td>Outcomes</td><td>Functional (BCVA)
Treatment-emergent adverse events</td></tr>
<tr><td>Analyses</td><td>Analysis of variance
T-test
Stratified and unstratified Cochran-Mantel-Haeszel tests</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
</table>

Bibliographic reference	Kaiser P K, Boyer D S, Cruess A F, Slakter J S, Pilz S, Weisberger A, and Group Denali Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study". Ophthalmology 119:1001-10.

Results

	Combined therapy (ranibizumab +SF PDT)	Intravitreal ranibizumab	Effect (95%CI)	Combined therapy (ranibizumab +RF PDT)	Intravitreal ranibizumab	Effect (95%CI)
Number of patients	104	112		105	112	
BCVA, Mean improvement (letters) from baseline						
Month 3 (SD)	+6.3 (14.2)	+6.9 (12.1)	-0.6 (-4.1, 2.9)	+6.4(11.7)	+6.9 (12.1)	-0.5 (-3.7, 2.7)
Month 12 (SD)	+5.3 (15.7)	+8.1 (15.1)	-2.8(-6.9, 1.3)	4.4 (15.5)	+8.1 (15.1)	-3.7(-7.8, 0.4)
% of patients did not lose vision at Month 12	74.7%	78.9%	0.9 (0.8, 1.1)	70.6%	78.9%	0.9 (0.8, 1,1)
% of patients gained ≥15 letters Month 12	31.3 (n=32)	41.1 (n=46)	0.75 (0.52, 1.08)	24.7 (n=26)	41.1 (n=46)	0.6 (0.4, 0.9)
CRT change from baseline						
Month 12	-151.7 (135.6)	-172.2 (166.7)	20.5 (-19.9, 60.9)	-140.9 (128.1)	-172.2 (166.7)	31.3 (-8.2, 70.8)

Bibliographic reference	Kaiser P K, Boyer D S, Cruess A F, Slakter J S, Pilz S, Weisberger A, and Group Denali Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study". Ophthalmology 119:1001-10.

	Additional treatment						
	Mean number of ranibizumab retreatment (month 3-11)	2.2	7.6		2.8	7.6	
	Mean number of PDT retreatment (month 3-11)	1.9	1.5		1.9	1.5	
	Total ocular AEs						
	No. of patients (%)	63 (60.6)	60 (54.1)	1.2 (0.89, 1.41)	56 (52.8)	60. (54.1)	0.98 (0.76, 1.25)

Missing data handling/loss to follow up	286 (89.1%) completed 12 months of the study
Was allocation adequately concealed?	Yes
Was knowledge of the allocated intervention adequately prevented during the study?	Yes
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	The trial was shortened from 24 to 12 months based on an early study's result (indicated no additional benefit of the combination treatment)
Were incomplete outcome data adequately addressed?	Unclear

Bibliographic reference	Kaiser P K, Boyer D S, Cruess A F, Slakter J S, Pilz S, Weisberger A, and Group Denali Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study". Ophthalmology 119:1001-10.
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Koh A, Lee W K, Chen L J, Chen S J, Hashad Y, Kim H, Lai T Y, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, and Lim T H. 2012. "EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy". Retina 32:1453-64.
Coutry/ies where the study carried out	7 study centres in Hong Kong, Singapore, South Korean, Taiwan, Thailand
Study type	Double blinded RCT
Aim of the study	To assess the effects of verteporfin photodynamic therapy (PDT) combined with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy
Study dates	Not reported
Sources of funding	Novartis Pharma AG Switzerland
Sample size	61
Inclusion Criteria	Treatment-naïve patients aged ≥18 years with symptomatic macular PCV Patients had BCVA letter score of 73 to 24 using ETDRS chart; Patients' eyes had a greatest linear dimension of the lesion of <5400um Patients had confirmed diagnosis of PCV by Central reading center
Exclusion Criteria	Patients had received treatment previously with verteporfin PDT, focal laser photocoagulation, transpupillary thermotherapy, pneumatic displacement of subretinal blood, or any investigational treatment; Patients had a history of angioid streaks, presumed ocular histoplasmosis syndrome, or pathological myopia Patients had experienced RPE tear, retinal detachment, macular hole, or uncontrolled glaucoma Patients underwent intraocular surgery (except uncomplicated cataract extraction with intraocular lens implantation within 60 days before the screening visit)

<table>
<tr><th>Bibliographic reference</th><td colspan="3">Koh A, Lee W K, Chen L J, Chen S J, Hashad Y, Kim H, Lai T Y, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, and Lim T H. 2012. "EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy". Retina 32:1453-64.</td></tr>
<tr><td>Baseline characteristics</td><td colspan="3"><table>
<tr><td></td><td>Verteportin PDT + ranibizumab</td><td>Ranibizumab</td></tr>
<tr><td>No. of patients</td><td>19</td><td>21</td></tr>
<tr><td>Mean aged (SD)</td><td>63.8 (8.3)</td><td>69.3 (8.3)</td></tr>
<tr><td>No. of females (%)</td><td>8 (42.1)</td><td>6 (28.6)</td></tr>
<tr><td>Mean total lesion areas, mm2(SD)</td><td>3.9 (5.5)</td><td>3.9 (2.5)</td></tr>
<tr><td>Mean polyp areas, mm2(SD)</td><td>0.3 (0.5)</td><td>0.2 (0.1)</td></tr>
<tr><td>Mean BCVA, letters (SD)</td><td>56.6 (20.9)</td><td>49.0 (18.1)</td></tr>
<tr><td>Mean CRT, µm (SD)</td><td>3347. (118.9)</td><td>268.5 (97.8)</td></tr>
<tr><td>No. patients with presence of leakage (%)</td><td>19 (100.0)</td><td>20 (95.2)</td></tr>
</table></td></tr>
<tr><td>Study procedures</td><td colspan="3">Eligible patients were randomised 1:1:1 for receiving verteporfin PDT plus intravitreal ranibizumab (0.5mg) (combination therapy), verteporfin alone or intravitreal ranibizumab (0.5mg) plus sham PDT
On day 1, patients received verteporfin PDT or sham PDT
On the same day, 1 to 24 hour after PDT, the patients were also administered a ranibizumab or sham injection
3 consecutive monthly ranibizumab intravitreal injections or sham were given starting at baseline
Re-treatments were given pro-re-nata according to the protocol specific re-treatment criteria evaluated by the investigator (mainly by ICGA assessed polyp regression)</td></tr>
<tr><td>Intervention</td><td colspan="3">verteporfin PDT plus intravitreal ranibizumab (0.5mg) (combination therapy)</td></tr>
<tr><td>Comparator</td><td colspan="3">intravitreal ranibizumab (0.5mg)</td></tr>
<tr><td>Outcomes</td><td colspan="3">Functional change: BCVA
Anatomical change: Central Foveal Thickness</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Koh A, Lee W K, Chen L J, Chen S J, Hashad Y, Kim H, Lai T Y, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, and Lim T H. 2012. "EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy". Retina 32:1453-64.</td></tr>
<tr><td></td><td>Adverse events</td></tr>
<tr><td>Length of follow up</td><td>6 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Verteportin PDT + ranibizumab (n=19)</td><td>Ranibizumab (n=21)</td><td>Effect between combination and Ranibizumab (95%CI)</td></tr>
<tr><td>BCVA change</td><td></td><td></td><td></td></tr>
<tr><td>Month 6</td><td>10.9 (10.9)</td><td>9.2 (12.4)</td><td>1.7 (-5.5, 8.9)</td></tr>
<tr><td>% of patients gaining ≥15 letters</td><td>21%</td><td>33.3%</td><td>0.6 (0.2, 1.8)</td></tr>
<tr><td>Central retinal thickness change</td><td></td><td></td><td></td></tr>
<tr><td>Month 6</td><td>-145.6 (119.0)</td><td>-65.7 (114.3)</td><td>-79.9 (-152.4, -7.42)</td></tr>
<tr><td>% patients with presence of leakage (n)</td><td>22.2% (n=4)</td><td>61.9% (n=13)</td><td>0.34 (0.13, 0.86)</td></tr>
<tr><td>Retreatment</td><td></td><td></td><td></td></tr>
<tr><td>Mean number of ranibizumab, month 3-5</td><td>1.1 (1.2)</td><td>2.2 (1.2)</td><td>-1.1 (-1.8, -0.4)</td></tr>
<tr><td>% of patients had ranibizumab, month3 -5</td><td>55.6%</td><td>81.0%</td><td>0.7 (0.5, 1.1)</td></tr>
<tr><td>Mean number of PDT, month 3-5</td><td>1.4 (0.5)</td><td>1.9 (0.3)</td><td>-0.5 (-0.8, -0.2)</td></tr>
<tr><td>% of patients had PDT, month3 -5</td><td>44.4%</td><td>90.5%</td><td>0.5 (0.3, 0.8)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Koh A, Lee W K, Chen L J, Chen S J, Hashad Y, Kim H, Lai T Y, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, and Lim T H. 2012. "EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy". Retina 32:1453-64.**
	Adverse events Ocular AEs: 5 / 4 / 1.4 (0.4, 4.4) Key non-ocular AEs: 6 / 7 / 0.9 (0.4, 2.3)
Missing data handling/loss to follow up	A total of 59 of 61 randomised patients completed the study.
Was allocation adequately concealed?	Unclear (no detailed description in the study)
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size for each group
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Krebs I, Vecsei Marlovits, V , Bodenstorfer J, Glittenberg C, Ansari Shahrezaei, S , Ristl R, and Binder S. 2013. "Comparison of Ranibizumab monotherapy versus combination of Ranibizumab with photodynamic therapy with neovascular age-related macular degeneration". Acta Opthalmologica 91:e178-83..
Coutry/ies where the study carried out	Austria
Study type	RCT
Aim of the study	Modern therapy of neovascular age-related macular degeneration consists in intravitreal injections of inhibitors of the vascular endothelial growth factor. An increasing number of these injections is required not only in monthly but also in as-needed treatment regimen. In this study, it should be examined whether an additional administered photodynamic therapy (PDT) can considerably reduce the number of injection.
Study dates	Not reported
Sources of funding	Novartis Pharma Austria
Sample size	48
Inclusion Criteria	age>50 years subfoveal CNV secondary to AMD predominantly classic lesions, and occult or minimally classic lesions with evidence of recent disease progression evidence that CNV extends under the geometric centre of the foveal avascular zone the areas of CNV must occupy at least 50% of the total lesion
Exclusion Criteria	patients who have a BCVA <33 letters in both eyes prior treatment in the study eye for nAMD concomitant use of chronic non-steroidal anti-inflammatory drugs or steroids for the duration of study participation any occult surgery within 6 months preceding day one, or a history of post-operative complications within the last 12 months preceding day one in the study eye history of uncontrolled glaucoma in the study eyes aphakia or absence of the posterior capsule in the study eye spherical equivalent of the refractive error in the study eye demonstrating more than -6 dioptres or an axial length of ≥26mm of myopia presence of a retinal pigment epithelial tear involving the macular in the study eye, angoid streaks or precursors of CNV in either eye due to other cause active intraocular inflammation in the study eye or any active infection involving an eyeball adnexa

<table>
<tr><th>Bibliographic reference</th><td>Krebs I, Vecsei Marlovits, V , Bodenstorfer J, Glittenberg C, Ansari Shahrezaei, S , Ristl R, and Binder S. 2013. "Comparison of Ranibizumab monotherapy versus combination of Ranibizumab with photodynamic therapy with neovascular age-related macular degeneration". Acta Opthalmologica 91:e178-83..</td></tr>
<tr><td></td><td>vitreous haemorrhage or history of rhegmatogenous retinal detachment or macular hole in the study eye</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Verteportin PDT + ranibizumab (group 2)</td><td>Ranibizumab (group 1)</td></tr>
<tr><td>No. of patients</td><td>20</td><td>24</td></tr>
<tr><td>Mean age (SD)</td><td>80.3 (6.3)</td><td>77.7 (8.9)</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>patients were randomised in 1:1 to one of 2 groups;
one group received 3 initial monthly ranibizumab (0.5mg) injection
the other group received an initial ranibizumab injection, a standard PDT one day thereafter and two further monthly ranibizumab injection
From month 3 to 12, patients of both groups received monthly ranibizumab injection unless BCVA worsened <5 letters compared to the BCVA at month 2 and retinal thickness at the central subfield as assessed by OCT</td></tr>
<tr><td>Intervention</td><td>Ranibizumab injection (0.5mg) plus a standard PDT</td></tr>
<tr><td>Comparator</td><td>Ranibizumab injection (0.5mg)</td></tr>
<tr><td>Outcomes</td><td>The number of ranibizumab injections
Mean change BCVA at month 3,6,12</td></tr>
<tr><td>Analyses</td><td>Descriptive statistics
Regression analyses</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Verteportin PDT + ranibizumab (n=20)</td><td>Ranibizumab (n=24)</td><td>Effect (95%CI)</td></tr>
<tr><td>Distance acuity change, letter</td><td></td><td></td><td></td></tr>
<tr><td>baseline</td><td>54.0 (18.4)</td><td>52.0 (21.6)</td><td>2.0 (-9.8, 13.8)</td></tr>
<tr><td>Month12</td><td>46.9 (28.3)</td><td>57.1 (24.6)</td><td>-10.2 (-26.3, 5.6)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Krebs I, Vecsei Marlovits, V , Bodenstorfer J, Glittenberg C, Ansari Shahrezaei, S , Ristl R, and Binder S. 2013. "Comparison of Ranibizumab monotherapy versus combination of Ranibizumab with photodynamic therapy with neovascular age-related macular degeneration". Acta Opthalmologica 91:e178-83..			
	% of patients lost ≥3 lines	31.6% (n=6)	9.1% (n=2)	3.60 (0.81, 15.91)
	Central retinal thickness change,µm			
	baseline	407.0 (124.5)	373.4 (91.0)	33.6 (-32.0, 99.2)
	Month 12	268.8 (90.8)	291.9 (70.0)	-23.1 (-71.6, 25.6)
	Ranibizumab injections			
	Mean number (SD)	4.7(1.8)	6.6(2.4)	-1.90 (-3.14, -0.66)
Missing data handling/loss to follow up	4 patients were screening failures and 3 patients withdrew their consent, 44 eyes of 44 patients included in the study.			
Was allocation adequately concealed?	Yes			
Was knowledge of the allocated intervention adequately prevented during the study?	Yes			
Was the allocation sequence adequately generated?	Yes			
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size			
Were incomplete outcome data adequately addressed?	Yes			
Are reports of the study free of suggestion of selective outcome reporting?	Yes			

Bibliographic reference	Kuppermann Baruch D, Goldstein Michaella, Maturi Raj K, Pollack Ayala, Singer Michael, Tufail Adnan, Weinberger Dov, Li Xiao-Yan, Liu Ching-Chi, Lou Jean, Whitcup Scott M, and Ozurdex Erie Study Group. 2015. "Dexamethasone Intravitreal Implant as Adjunctive Therapy to Ranibizumab in Neovascular Age-Related Macular Degeneration: A Multicenter Randomized Controlled Trial". Ophthalmologica 234:40-54.
Coutry/ies where the study carried out	Multiple sites
Study type	Single-blinded RCT
Aim of the study	To evaluate the efficacy and safety of dexamethasone intravitreal implant 0.7 mg (DEX) as adjunctive therapy to ranibizumab in neovascular age-related macular degeneration (nvAMD).
Study dates	Not reported
Sources of funding	Allergan Inc
Sample size	310 screened and received the first protocol-mandated ranibizumab injections
Inclusion Criteria	≥50 years of age Subfoveal CNV secondary to nAMD Required ranibizumab therapy for treatment of nAMD Patients' eyes had total size of the lesion ≤12 macular photocoagulation study disc areas Patients' active CNV representing ≥50% of the areas of the lesion Patients' BCVA ≥19 and ≤69 letter using ETDRS method
Exclusion Criteria	Patients were with glaucoma, diabetic retinopathy Patients had active ocular infection at screening or the baseline visit Patients had a history of an increased IOP in response to steroid treatment that was ≥10mm Hg and reached a level of ≥ 25mmHg or that required treatment with laser, surgery, or >1 IOP lowering medication Patients had subfoveal scarring, fibrosis or atrophy Patients had retinal pigment epithelium tear that included the fovea Patients had presence of any causes of CNV other than nvAMD or any other ocular disease that could compromise intraocular lens Patients had a history of pars plana vitrectomy Patients currently treat with ≥2 IOP lowering medications Screening or baseline IOP>23mmHg if untreated or >21mmHg if treated with 1 IOP-lowering medication

<table>
<tr><th>Bibliographic reference</th><td>Kuppermann Baruch D, Goldstein Michaella, Maturi Raj K, Pollack Ayala, Singer Michael, Tufail Adnan, Weinberger Dov, Li Xiao-Yan, Liu Ching-Chi, Lou Jean, Whitcup Scott M, and Ozurdex Erie Study Group. 2015. "Dexamethasone Intravitreal Implant as Adjunctive Therapy to Ranibizumab in Neovascular Age-Related Macular Degeneration: A Multicenter Randomized Controlled Trial". Ophthalmologica 234:40-54.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Treatment-naïve cohort</td><td></td></tr>
<tr><td></td><td>DEX implant + ranibizumab</td><td>ranibizumab</td></tr>
<tr><td>Number of patients</td><td>58</td><td>57</td></tr>
<tr><td>Age, years</td><td>77.4 (9.5)</td><td>77.4 (7.1)</td></tr>
<tr><td>No. of female (%)</td><td>37 (63.8)</td><td>35 (61.4)</td></tr>
<tr><td>No. of patients had PED (%)</td><td>20 (34.5)</td><td>22 (38.6)</td></tr>
<tr><td>No. of patients had RAP (%)</td><td>4 (6.9)</td><td>3 (5.3)</td></tr>
<tr><td>Duration of CNV, months</td><td>4.9 (10.3)</td><td>4.1 (14.0)</td></tr>
<tr><td>Central retinal subfield thickness, µm</td><td>262.5 (98.9)</td><td>276.7 (133.7)</td></tr>
<tr><td>BCVA, letter</td><td>55.4 (15.5)</td><td>56.5 (13.3)</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Eligible patients were treated with ranibizumab (0.5mg) in the study eye
Four week later, at the baseline study visit, the need for re-treatment of the study eye was evaluated by OCT and clinical examination
Patients who demonstrated the following criteria were eligible for re-treatment:
Macular cysts
Subreitnal fluid
Pigment epithelial detachment
A ≥50um increase in the central retinal subfield mean thickness from the lowest measurement at the previous visit
New subretinal haemorrhage
Patients were randomised at the baseline visit in a 1:1 allocation to DEX implant (0.7mg) or sham procedure
At the next study visit (day 7-14), all randomised patients received a second protocol-mandated intravitreal ranibizumab injections (0.5mg)
For patients who still met the study defined retreatment criteria, up to 5 additional ranibizumab injections were administered during the outcome assessment visits at week 5,9,13,17, 21.</td></tr>
<tr><td>Intervention</td><td>Dexamethasone Intravitreal Implant (0.7mg) and Ranibizumab (0.5mg)</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Kuppermann Baruch D, Goldstein Michaella, Maturi Raj K, Pollack Ayala, Singer Michael, Tufail Adnan, Weinberger Dov, Li Xiao-Yan, Liu Ching-Chi, Lou Jean, Whitcup Scott M, and Ozurdex Erie Study Group. 2015. "Dexamethasone Intravitreal Implant as Adjunctive Therapy to Ranibizumab in Neovascular Age-Related Macular Degeneration: A Multicenter Randomized Controlled Trial". Ophthalmologica 234:40-54.</td></tr>
<tr><td>Comparator</td><td>Intravitreal ranibizumab injections (0.5mg)</td></tr>
<tr><td>Outcomes</td><td>ranibizumab injections free interval (time from the second protocol-mandated ranibizumab injections to determination of eligibility to receive the first as-needed ranibizumab injections)
BCVA in both eyes
Central retinal subfield thickness
Adverse events</td></tr>
<tr><td>Analyses</td><td>The analyses of efficacy variables were based on the intent-to-treat patient population;
The ranibizumab injection-free interval used Kaplan-Meier method;
Cochran-Mantel-Haenzel test
Pearson chi-square</td></tr>
<tr><td>Length of follow up</td><td>25 weeks</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Treatment-naïve cohort</td><td></td><td></td></tr>
<tr><td></td><td>DEX implant + ranibizumab</td><td>Ranibizumab</td><td>Effect (95%CI)</td></tr>
<tr><td>Number of patients</td><td>58</td><td>57</td><td></td></tr>
<tr><td>Median of injection free interval, days</td><td>34</td><td>29</td><td></td></tr>
<tr><td>Ranibizumab injection</td><td>4.4 (1.7)</td><td>4.9 (1.7)</td><td>-0.5 (-1.1, 0.1)</td></tr>
<tr><td>BCVA(ETDRS0 change from baseline to week 25</td><td>1.5 (10.6)</td><td>2.6 (8.4)</td><td>-1.1 (-4.6, 2.4)</td></tr>
<tr><td>Number of patients had BCVA ≥10 letter improvement</td><td>11 (19.0%)</td><td>9 (15.8)</td><td>1.2 (0.5, 2.7)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Kuppermann Baruch D, Goldstein Michaella, Maturi Raj K, Pollack Ayala, Singer Michael, Tufail Adnan, Weinberger Dov, Li Xiao-Yan, Liu Ching-Chi, Lou Jean, Whitcup Scott M, and Ozurdex Erie Study Group. 2015. "Dexamethasone Intravitreal Implant as Adjunctive Therapy to Ranibizumab in Neovascular Age-Related Macular Degeneration: A Multicenter Randomized Controlled Trial". Ophthalmologica 234:40-54.
	Number of patients had BCVA ≥15 letter improvement: 4 (6.9); 5 (8.8); 0.7 (0.2, 2.8) CRT changes from baseline to week 25,µm: -12.61 (96.4); -34.7 (106.6); 22.1 (-15.1, 59.3)
Missing data handling/loss to follow up	67 patients either failed to meet retreatment criteria (n=31) or were ineligible for the study for other reason (n=36).
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Short follow-up time
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

<table>
<tr><th>Bibliographic reference</th><th>Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A, and Group Mont Blanc Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results". Ophthalmology 119:992-1000.</th></tr>
<tr><td>Coutry/ies where the study carried out</td><td>12 European countries</td></tr>
<tr><td>Study type</td><td>Prospective, multicentre, double-masked, randomized, active-controlled trial</td></tr>
<tr><td>Aim of the study</td><td>To compare the efficacy and safety of same-day verteporfin photodynamic therapy (PDT) and intravitreal ranibizumab combination treatment versus ranibizumab monotherapy in neovascular age-related macular degeneration.</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Sources of funding</td><td>Novartis Pharma AG, Basel, Switzerland</td></tr>
<tr><td>Sample size</td><td>255</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients aged ≥50 years with a diagnosis of AMD related active subfoveal choroidal neovascularization;
The total area of CNV encompassed within the lesion had to be≥50% of the total lesion area, with the largest linear dimension of the total lesion area ≤ 5400µm
BCVA of the study eye between 73 and 24 letters</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients had prior treatment for neovascular AMD in the study eye
Patients had angioid streaks
Patients had presumed ocular histoplasmosis syndrome
Patients had pathologic myopia, CNV not from AMD, retinal pigment epithelium tear or uncontrolled glaucoma
Patients had presence of fibrosis, haemorrhage, retinal pigment epithelium detachment or other hypofluorescent areas obscuring >50% of the whole lesion</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Verteporfin PDT + ranibizumab (n=122)</td><td>Ranibizumab (n=133)</td></tr>
<tr><td>Mean age, years (SD)</td><td>76.8 (7.7)</td><td>75.5 (7.4)</td></tr>
<tr><td>N (%) male</td><td>44 (36.1)</td><td>59 (44.4)</td></tr>
<tr><td>Baseline BCVA, mean letters</td><td>54.6 (13.4)</td><td>55(12.3)</td></tr>
<tr><td>Lesion type, n(%)</td><td></td><td></td></tr>
<tr><td>Predominantly classic</td><td>50 (41.0)</td><td>57 (42.9)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A, and Group Mont Blanc Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results". Ophthalmology 119:992-1000.**
	Minimally classic: 20 (16.4) / 25 (18.8) Occult with no classic: 51 (41.8) / 51 (38.3)
Study procedures	Patients were randomised in a 1:1 ratio to either combination treatment or ranibizumab monotherapy (0.5mg) On day 1, patients received verteporfin or sham infusion followed by laser application at standard fluence PDT On the same day, ranibizumab (0.5mg) was injected 1 hour after the start of verteporfin PDT Ranibizumab treatment was to be repeated at month 1 and 2. The need for re-treatment was determined by the investigator based on functional and anatomic parameter, including a≥100-µm increase in central retinal thickness from the lowest previous value, presence of subretinal fluid or haemorrhage, BCVA decrease of >5 letter, and leakage on FA.
Intervention	Verteporfin photodynamic therapy (PDT) and intravitreal ranibizumab combination treatment
Comparator	Ranibizumab monotherapy
Outcomes	Visual acuity Central retinal thickness Incidence of ocular and non-ocular AEs
Analyses	Descriptive statistics
Length of follow up	12 months
Results	See table below

	Verteporfin PDT + ranibizumab (n=121)	Ranibizumab (n=132)	Effect (95%CI)
BCVA, letter			
Baseline (SD)	54.6 (13.5)	55.1 (12.3)	-0.5 (-3.7, 2.7)
Month12	57.1 (18.3)	59.4 (18.8)	-2.3 (-6.9, 2.3)
Change	2.5 (14.8)	4.4 (15.9)	-1.9 (-5.7, 1.9)
% of patients gained≥15 letters	18.2 (n=22)	25.8 (n=34)	0.71 (0.44, 1.14)

Bibliographic reference	Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A, and Group Mont Blanc Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results". Ophthalmology 119:992-1000.			
	% of patients gained≥10 letters	37.2 (n=45)	38.6 (n=51)	0.96 (0.70, 1.32)
	% of patients gained≥5 letters	50.4 (n=61)	52.3 (n=69)	0.96 (0.76, 1.23
	% of patients gained≥0 letters	71.1 (n=86)	65.9 (n=87)	1.08 (0.91, 1.27)
	% of patients loss< 15 letters	86.8 (n=105)	90.9 (n=120)	0.95 (0.87, 1.04)
	% of patients loss< 30 letters	95.9 (n=116)	96.2 (n=127)	1.00 (0.95, 1.05)
	Central retinal thickness change, µm			
	Baseline to Month 12	-115.3 (99.0)	-10.7.7 (126.3.0)	-7.6 (-35.4, 20.3)
	Re-treatment			
	% of patients had treatment free intervals≥3 months at appoint after Month2	96 (n=116)	92 (n=121)	1.05 (0.98, 1.11)
	% of patients did not receive ranibizumab retreatment	29.5 (n=36)	24.1(n=32)	1.23 (0.82, 1.84)
	Mean number of ranibizumab injections	4.8 (2.0)	5.1 (2.0)	-0.30 (-0.79, 0.19)
	No. o4.f ranibizumab retreatment, mean (SD)	1.9 (2.0)	2.2 (2.0)	-0.3 (-0.8, 0.2)
	Mean number of PDT sessions (SD)	1.7 (0.8)	1.9 (0.9)	-0.20 (-0.41, 0.01)

Bibliographic reference	Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A, and Group Mont Blanc Study. 2012. "Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results". Ophthalmology 119:992-1000.
	<table><tr><td>No. of verteporfin PDT retreatment, mean (SD)</td><td>0.7</td><td>0.9</td><td></td></tr><tr><td>Reported adverse events</td><td></td><td></td><td></td></tr><tr><td>No. of Ocular AEs (%)</td><td>51 (41.8)</td><td>54 (40.6)</td><td>1.0 (0.8, 1.4)</td></tr><tr><td>Non-ocular AEs</td><td>66 (54.1)</td><td>70 (52.6)</td><td>1.0 (0.8, 1.3)</td></tr></table>
Missing data handling/loss to follow up	255 randomised in the study, and 240 patients (94%) completed 12 months
Was allocation adequately concealed?	Yes
Was knowledge of the allocated intervention adequately prevented during the study?	Yes
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Patients in monotherapy group had slightly larger lesion size
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

<table>
<tr><th>Bibliographic reference</th><th>Lazic R, and Gabric N. 2007. "Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration". Ophthalmology 114:1179-85.</th></tr>
<tr><td>Coutry/ies where the study carried out</td><td>Saudi Arabia</td></tr>
<tr><td>Study type</td><td>Controlled, open label randomised RCT</td></tr>
<tr><td>Aim of the study</td><td>To evaluate the efficacy and safety of photodynamic therapy (PDT) with verteporfin combined with intravitreal bevacizumab in choroidal neovascularization (CNV) owing to age-related macular degeneration (AMD) in comparison with individual monotherapies used as controls.</td></tr>
<tr><td>Study dates</td><td>Feb 6 2006 to June 28 2006</td></tr>
<tr><td>Sources of funding</td><td>Not reported</td></tr>
<tr><td>Sample size</td><td>156</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients aged 50 years and/or over with minimally classic or occult CNV due to AMD in 1 or both eyes;
Studies eye had never been treated
Patients had active leakage documented by FA and OCT, subfoveal lesion, greatest linear diameter of lesion ≤7500μm
Patients had BCVA≥20/400 (ETDRS chart)
Patients had a presumed evidence of disease progression defined as a deterioration of BCVA≥5 letters and increase of lesion size ≥10% within the 3 months before randomisation</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients with cataract or media opacities that could significantly interfere with OCT imaging and image analysis
Patients with retinal angiomatous proliferation or polypoidal choroidal vasculopathy in studied or fellow eye
Patients had ocular surgery within the 3 months before randomisation
Patients had a history of uveitis
Patients had rise of intraocular pressure ≥25mmHg
Patients had glaucoma visual field loss in the studies eye</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>COMB</td><td>BEV</td></tr>
<tr><td>Number of patients</td><td>52</td><td>54</td></tr>
<tr><td>Age, mean (SD)</td><td>75.4 (6.3)</td><td>76.1 (5.9)</td></tr>
<tr><td>M/F</td><td>18/34</td><td>17/37</td></tr>
<tr><td>Size of lesion, μm</td><td>3982 (1927)</td><td>3784 (1387)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Lazic R, and Gabric N. 2007. "Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration". Ophthalmology 114:1179-85.
	Fellow eye status No. of Dry AMD (%): 24 (46); 23 (43) Scar AMD: 23 (44); 25 (46) Wet AMD: 5 (10); 6 (11) CNV characteristics Minimally classic: 42 (81); 44 (82) Occult: 10 (19); 10 (18)
Study procedures	All patients underwent a complete ophthalmatic examination at the screening visit At the baseline visit (within 3 weeks after the screening), eligible patients were randomly allocated to treatment groups: verteporfin PDT group, intravitreal bevacizumab (BEV) group, and their combination group (COMB) Patients who were allocated to PDT and COMB groups were administered verteporfin PDT Patients in the BEV and COMB groups were administered bevacizumab (1.25mg), and administration of bevacizumab in the COMB group was performed immediately (within 1 hour) after verteporfin PDT Patients were followed up 1 and 3 months after administrations of the treatments
Intervention	photodynamic therapy (PDT) with verteporfin combined with intravitreal bevacizumab
Comparator	intravitreal bevacizumab monotherapy
Outcomes	Best-corrected visual acuity Central foveal thickness
Analyses	Descriptive statistics Mix procedure from SAS
Length of follow up	3 months
Results	Verteporfin PDT +bevacizumab (n=52); Bevacizumab (n=54) BCVA, logMAR baseline: 1.06 (1.02,1.10); 1.09 (1.05,1.13)

Bibliographic reference	Lazic R, and Gabric N. 2007. "Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration". Ophthalmology 114:1179-85.
	Change Month1 | 0.25 (0.21, 028) | 0.17 (0.14, 0.20) Change Month3 | 0.22 (0.20,0.25) | 0.08 (0.05, 0.10) Central foveal thickness, µm | | baseline | 349.1 (339.3, 358.8) | 355.1 (345.5, 364.7) Change Month1 | -64.5 (-74.3, -54.7) | -54.7 (-64.3, -45.0) Change Month3 | -59.6 (-68.7, -50.4) | -34.0 (-43.0, -25.0) Adverse events | | No. of patients, pigment epithelial tear | 0 | 3 Posterior vitreous detachments | 4 | 8 Cataract progression | 3 | 4
Missing data handling/loss to follow up	281 were screened ,and 156 completed follow-up
Was allocation adequately concealed?	Open label (not described in the study)
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	Short follow-up period

Bibliographic reference	Lazic R, and Gabric N. 2007. "Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration". Ophthalmology 114:1179-85.
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Lim J Y, Lee S Y, Kim J G, Lee J Y, Chung H, and Yoon Y H. 2012. "Intravitreal bevacizumab alone versus in combination with photodynamic therapy for the treatment of neovascular maculopathy in patients aged 50 years or older: 1-year results of a prospective clinical study". Acta Opthalmologica 90:61-7.
Coutry/ies where the study carried out	Korea
Study type	RCT
Aim of the study	To compare the outcomes of treatment with intravitreal bevacizumab alone (BEVA group) or in combination with photodynamic therapy (PDT) (COMB group), in patients aged at least 50 years with neovascular maculopathy.
Study dates	July 2006
Sources of funding	Not reported
Sample size	47
Inclusion Criteria	Age 50 years or older BCVA of 0.6 or worse in the study eye
Exclusion Criteria	Intravitreal triamcinolone (IVTA) within 90 days prior to screening PDT within 30 days before screening A history of ocular surgery within 90 days prior to screening A history of vitreous haemorrhage, retinal tear, retinal detachment, macular hole or retinal vein obstruction Severe intraocular inflammation or infection within 30 days before screening Diabetic retinopathy Aphakia Systemic conditions including thromboembolism, previous myocardial infarction or prior cerebral vascular accident

<table>
<tr><th>Bibliographic reference</th><td colspan="2">Lim J Y, Lee S Y, Kim J G, Lee J Y, Chung H, and Yoon Y H. 2012. "Intravitreal bevacizumab alone versus in combination with photodynamic therapy for the treatment of neovascular maculopathy in patients aged 50 years or older: 1-year results of a prospective clinical study". Acta Opthalmologica 90:61-7.</td></tr>
<tr><td>Baseline characteristics</td><td colspan="2"><table>
<tr><td></td><td>COMB</td><td>BEVA</td></tr>
<tr><td>Number</td><td>23</td><td>18</td></tr>
<tr><td>Mean age, years</td><td>66.3</td><td>70.9</td></tr>
<tr><td>Mean BCVA, logMAR</td><td>1.05</td><td>1.03</td></tr>
</table></td></tr>
<tr><td>Study procedures</td><td colspan="2">Patients were randomised into either an intravitreal bevacizumab monotherapy (BEVA group) or a combination therapy group (COMB group).
Intravitreal bevacizumab (1.25mg) was injected into all patients at 6 weeks intervals; a total of 3 injections were usually given.
In the combination group, PDT was performed in association with one of the 3 injections; administration of bevacizumab was performed within 7 days before or after PDT
Patients were followed-up 1 and 6 week after every bevacizumab injection during the first 18 weeks, and then at 3-month intervals.</td></tr>
<tr><td>Intervention</td><td colspan="2">PDT + bevacizumab</td></tr>
<tr><td>Comparator</td><td colspan="2">Bevacizumab monotherapy</td></tr>
<tr><td>Outcomes</td><td colspan="2">Best-corrected visual acuity
Central foveal thickness</td></tr>
<tr><td>Analyses</td><td colspan="2">Repeated measures
Fisher’s exact test</td></tr>
<tr><td>Length of follow up</td><td colspan="2">12 months</td></tr>
<tr><td>Results</td><td colspan="2"><table>
<tr><td></td><td>COMB (n=23)</td><td>BEVA (n=18)</td></tr>
<tr><td>No. of patients had additional bevacizumab</td><td>5</td><td>4</td></tr>
<tr><td>Visual acuity (lines gained)</td><td>2.43 (2.83)</td><td>3 (3.35)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Lim J Y, Lee S Y, Kim J G, Lee J Y, Chung H, and Yoon Y H. 2012. "Intravitreal bevacizumab alone versus in combination with photodynamic therapy for the treatment of neovascular maculopathy in patients aged 50 years or older: 1-year results of a prospective clinical study". Acta Opthalmologica 90:61-7.
	No of bevacizumab treatments: 3.25 (0.58) / 3.2 (0.42)
Missing data handling/loss to follow up	6 were lost to follow up during the study
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Unclear

Bibliographic reference	Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.
Coutry/ies where the study carried out	Iran
Study type	RCT

Bibliographic reference	**Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.**
Aim of the study	To compare the outcomes of photodynamic therapy (PDT) combined with intravitreal bevacizumab (IVB) with versus without intravitreal triamcinolone (IVT) in neovascular age-related macular degeneration (AMD).
Study dates	Not reported
Sources of funding	Not reported
Sample size	84 patients (84 eyes)
Inclusion Criteria	Patients with subfoveal CNV of all types (predominantly classic, minimally classic, occult and retinal angiomatous proliferation) secondary to AMD and no history of prior treatment
Exclusion Criteria	Patients with presence of diabetic retinopathy, glaucoma, or any macular disease other than AMD
Baseline characteristics	

	Triple therapy (PDT+IVT+IVB)	Dual therapy (PDT+IVB)	P values
Number of patients	42	42	
Mean age, years (SD)	69.9 (9.1)	71.7 (9.0)	0.358
Male/female	25/17	23/19	0.659
CNV types, n(%)			0.503
Minimally classic	4 (9.5)	9 (21.4)	
Dominantly classic	10 (23.8)	9 (21.4)	
Occult	12 (31.0)	12 (28.6)	
RAP/RCA	15 (35.7)	12 (28.6)	
PED, n(%)	25 (59.5)	24 (57.1)	0.825
CNV size, n(%)			0.395
<2	19 (45.2)	22 (52.4)	
2-4	15 (35.7)	14 (33.3)	
>4	8 (19.1)	6 (13.3)	
Mean BCVA, logMAR	0.80 (0.40)	0.87 (0.39)	0.411

Bibliographic reference	**Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.**
	Mean CMT, µm (SD) 335 (116) 341 (140) 0.829 Mean IOP mmHg (SD) 15.2 (2.5) 15.2 (2.9) 0.992
Study procedures	Eligible patients were randomly assigned to receive verteporfin PDT plus intravitreal bevacizumab (IVB) or a combination of PDT and bevacizumab/triamcinolone(IVB/IVT) Patients in the dual treatment groups underwent standard PDT followed by intravitreal bevacizumab (1.25mg) after 48 hour; In the triple treatment group, 2mg triamcinolone acetonide was injected intravitreally in addition to PDT and bevacizumab; All patients were examined the 1st day after injection particularly for signs of intraocular inflammation Need for re-treatment with IVC injection was first evaluated at week 12. Additional IVB injections were given eyes with active CNV according to clinical findings (including decrease in VA and/or haemorrhage on fundus examinations), and/or fluid on OCT, and/or persistence or reoccurrence of dye leakage on FA. Either PDT or IVT injection were not repeated during the follow-up period.
Intervention	Photodynamic therapy (PDT) combined with intravitreal bevacizumab (IVB) with intravitreal triamcinolone (IVT)
Comparator	Photodynamic therapy (PDT) combined with intravitreal bevacizumab (IVB) without intravitreal triamcinolone (IVT)
Outcomes	Change in BCVA from baseline Change in central macular thickness The need for additional injections Time interval up to the first retreatment
Analyses	Intention to treat On treatment (per-protocol) analyses Chi-square Fisher’s exact test Mann-Whitney test Analysis of covariance
Length of follow up	12 months

Bibliographic reference	Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.

Results

	Triple therapy (PDT+IVT+IVB)	Dual therapy(PDT+IVB)	Effect (95%CI)
Number of patients	42	42	
BCVA change from baseline, logMAR			
Week 6	-0.12 (0.25)	-0.14 (0.21)	-0.02 (-0.12, 0.08)
Week12	-0.16 (0.29)	-0.16 (0.22)	0 (-0.11, 0.12)
Week 20	-0.17 (0.27)	-0.18 (0.23)	0 (-0.11, 0.11)
Week 24	-0.2 (0.3)	-0.17 (0.33)	0.03 (-0.11, 0.17)
Week 36	-0.17 (0.33)	-0.15 (0.33)	0.02 (-0.12, 0.17)
Week 54	-0.16 (0.36)	-0.15 (0.36)	0.01 (-0.15,0.17)
Central macular thickness change, µm			
Week 6	-102 (109)	-112 (128)	-11 (71,50)
Week12	-92 (107)	-114 (146)	-11 (-87,44)
Week 20	-91 (109)	-100 (143)	-9 (-75, 56)

Bibliographic reference	Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.
	<table><tr><td>Week 24</td><td>-82 (128)</td><td>-92 (150)</td><td>-10 (-81,61)</td></tr><tr><td>Week 36</td><td>-90 (133)</td><td>-91 (153)</td><td>-1 (-74, 72)</td></tr><tr><td>Week 54</td><td>-72 (125)</td><td>-105 (143)</td><td>-33 (-102,35)</td></tr><tr><td>Retreatment</td><td></td><td></td><td></td></tr><tr><td>Men (SD)</td><td>0.9 (0.9)</td><td>1.3 (1.1)</td><td>-0.40 (-0.83, 0.03)</td></tr><tr><td>% eye no need of retreatment within 12 months</td><td>38.1 (n=16)</td><td>26.2 (n=11)</td><td>1.45 (0.77, 2.75)</td></tr><tr><td>Median time to first re-treatment, weeks (95%CI)</td><td>25.1 (17.1,33.2)</td><td>15.6 (14.7, 16.4)</td><td></td></tr></table> No systematic AEs were reported
Missing data handling/loss to follow up	84 patients recruited, and 63 completed 6-month follow-up, 51 completed 12 month follow-up
Was allocation adequately concealed?	Yes
Was knowledge of the allocated intervention adequately prevented during the study?	Yes
Was the allocation sequence adequately generated?	Yes

Bibliographic reference	Piri Niloofar, Ahmadieh Hamid, Taei Ramin, Soheilian Masoud, Karkhaneh Reza, Lashay Alireza, Golbafian Faegheh, Yaseri Mehdi, and Riazi-Esfahani Mohammad. 2014. "Photodynamic Therapy and Intravitreal Bevacizumab with Versus without Triamcinolone for Neovascular Age-related Macular Degeneration; a Randomized Clinical Trial". Journal of Ophthalmic & Vision Research 9:469-77.
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Ranchod T M, Ray S K, Daniels S A, Leong C J, Ting T D, and Verne A Z. 2013. "LuceDex: a prospective study comparing ranibizumab plus dexamethasone combination therapy versus ranibizumab monotherapy for neovascular age-related macular degeneration". Retina 33:1600-4.
Coutry/ies where the study carried out	USA
Study type	Single-blinded RCT
Aim of the study	The LuceDex prospective randomized pilot trial compared the combination of intravitreal ranibizumab and dexamethasone with ranibizumab monotherapy for treatment of neovascular age-related macular degeneration
Study dates	Trial registered May 2011
Sources of funding	Not reported
Sample size	40 patients
Inclusion Criteria	Patients were aged ≥50 year, with BCVA of 20/32 to 20/400 and neovascular AMD in the study eye
Exclusion Criteria	Patients had previous treatment for AMD in the study eye Patients had previous intravitreal drug delivery in the study eye Patients had previous vitrectomy in the study eye Patients had fibrosis or atrophy involving the centre of the foveal in the study eye

<table>
<tr><th>Bibliographic reference</th><td>Ranchod T M, Ray S K, Daniels S A, Leong C J, Ting T D, and Verne A Z. 2013. "LuceDex: a prospective study comparing ranibizumab plus dexamethasone combination therapy versus ranibizumab monotherapy for neovascular age-related macular degeneration". Retina 33:1600-4.</td></tr>
<tr><td></td><td>Neovascular membrane from other concurrent retinal disease
Patients had history of glaucoma filtering surgery in the study eye
Patients had active co-existing macular disease
Patients had active intraocular inflammation in the study eye
Patients had history of allergy to fluorescein not amenable to treatment</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Combination group (Group 1)</th><th>Monotherapy group (Group 2)</th><th>p</th></tr>
<tr><td>Number of patients</td><td>17</td><td>20</td><td></td></tr>
<tr><td>Male, n(%)</td><td>7 (41)</td><td>6 (30)</td><td>0.72</td></tr>
<tr><td>Mean age, years</td><td>79.5</td><td>82.7</td><td>0.09</td></tr>
<tr><td>Mean BCVA (ETDRS letters)</td><td>61.9</td><td>55.6</td><td>0.10</td></tr>
<tr><td>Mean CMT, µm</td><td>342.2</td><td>291.9</td><td>0.17</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were randomised 1:1 to combination therapy or monotherapy
Combination group received treatment comprised of intravitreal dexamethasone (500µg) followed by intravitreal ranibizumab (0.5mg)
Monotherapy group received only intravitreal ranibizumab (0.5mg)
Study eyes in both groups received the study treatment monthly for 4 months followed by treatment on indication
Retreatment criteria: any biomicroscopic/ angiographic evidence of subretinal haemorrhage, subretinal fluid, or cystoid macular oedema, appearance of new subretinal haemorrhage, or lesion activity, or any evidence by OCT of increased CFT, subretinal haemorrhage, subretinal fluid, or cystoid macular oedema. Combination group were given subsequent treatment with ranibizumab alone if IOP rose>30 mmHg.</td></tr>
<tr><td>Interventio</td><td>Combination of intravitreal ranibizumab and dexamethasone</td></tr>
<tr><td>Comparator</td><td>Ranibizumab monotherapy</td></tr>
<tr><td>Outcomes</td><td>Best-corrected visual acuity
Central macular thickness</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="4">Ranchod T M, Ray S K, Daniels S A, Leong C J, Ting T D, and Verne A Z. 2013. "LuceDex: a prospective study comparing ranibizumab plus dexamethasone combination therapy versus ranibizumab monotherapy for neovascular age-related macular degeneration". Retina 33:1600-4.</td></tr>
<tr><td>Analyses</td><td colspan="4">Chi-square
Two sample T test</td></tr>
<tr><td>Length of follow up</td><td colspan="4">12 months</td></tr>
<tr><td>Results</td><td colspan="4"><table>
<tr><td></td><td>Combination group (Group 1)</td><td>Monotherapy group (Group 2)</td><td>Effect (95%CI)</td></tr>
<tr><td>Number of patients</td><td>17</td><td>20</td><td></td></tr>
<tr><td>Visual acuity</td><td></td><td></td><td></td></tr>
<tr><td>Gain of ≥ 0 letter to Month 12, n(%)</td><td>15 (88)</td><td>14 (70)</td><td>1.26 (0.90, 1.76)</td></tr>
<tr><td>Gain ≥ 15 letters</td><td>6 (35)</td><td>4 (20)</td><td>1.76 (0.59, 5.24)</td></tr>
<tr><td>Mean visual gain, letters</td><td>11.1</td><td>5.9</td><td></td></tr>
<tr><td>Mean number of treatments</td><td>7.1</td><td>6.6</td><td></td></tr>
<tr><td>CMT changes,ųm</td><td>-130.6</td><td>-90.2</td><td></td></tr>
</table></td></tr>
<tr><td>Missing data handling/loss to follow up</td><td colspan="4">37 out of 40 patients completed 12 month follow-up</td></tr>
<tr><td>Was allocation adequately concealed?</td><td colspan="4">Unclear</td></tr>
<tr><td>Was knowledge of the allocated intervention adequately prevented during the study?</td><td colspan="4">Unclear</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td colspan="4">Unclear</td></tr>
</table>

Bibliographic reference	Ranchod T M, Ray S K, Daniels S A, Leong C J, Ting T D, and Verne A Z. 2013. "LuceDex: a prospective study comparing ranibizumab plus dexamethasone combination therapy versus ranibizumab monotherapy for neovascular age-related macular degeneration". Retina 33:1600-4.
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Semeraro F, Russo A, Delcassi L, Romano M R, Rinaldi M, Chiosi F, and Costagliola C. 2015. "Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy". Retina 35:1547-54.
Coutry/ies where the study carried out	Not reported
Study type	Open label RCT
Aim of the study	To evaluate whether ketorolac eye drops plus intravitreal ranibizumab (IVR) or verteporfin photodynamic therapy plus IVR provides additional benefit over IVR monotherapy for treatment of choroidal neovascularization in age-related macular degeneration.
Study dates	University hospital of Brescia and Naples
Sources of funding	Not reported
Sample size	75
Inclusion Criteria	Patients were older than 40 years Presence of treatment-naïve neovascular AMD Evidence of leakage on FA and fluid on OCT as indications of new active CNV
Exclusion Criteria	Any previous intravitreal treatment Previous laser treatment in the study eye

<table>
<tr><th>Bibliographic reference</th><td colspan="4">Semeraro F, Russo A, Delcassi L, Romano M R, Rinaldi M, Chiosi F, and Costagliola C. 2015. "Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy". Retina 35:1547-54.</td></tr>
<tr><td></td><td colspan="4">Myopia more than 7 diopters in the study eye
Concurrent eye disease in the study eye that could compromise visual acuity
Concurrent corneal epithelial disruption or any condition that would affect the ability of the cornea to heal
Known sensitivity to any component of the formulation being investigated</td></tr>
<tr><td>Baseline characteristics</td><td colspan="4"><table>
<tr><td></td><td>PDT + ranibizumab</td><td>Ranibizumab (IVR) + off-label topical ketorolac eye drop</td><td>Ranibizumab</td></tr>
<tr><td>Number of patients</td><td>25</td><td>25</td><td>25</td></tr>
<tr><td>No. of male (%)</td><td>11 (44)</td><td>13 (48)</td><td>12(48)</td></tr>
<tr><td>Mean age (SD)</td><td>76.6 (6.2)</td><td>76.3 (9.7)</td><td>77.2 (8.3)</td></tr>
<tr><td>Visual acuity, logMAR</td><td>0.59 (0.20)</td><td>0.60 (0.24)</td><td>0.61 (0.30)</td></tr>
<tr><td>CMT, um</td><td>439 (73.5)</td><td>420 (87.2)</td><td>440 (84.0)</td></tr>
<tr><td>N (%) classic/predominantly classic</td><td>12 (48)</td><td>10 (40)</td><td>11 (44)</td></tr>
<tr><td>N (%) minimally classic/occult</td><td>13 (52)</td><td>15 (60)</td><td>14 (56)</td></tr>
</table></td></tr>
<tr><td>Study procedures</td><td colspan="4">Patients were randomised to 3 groups;
Group 1(RM): patients received intravitreal 0.5mg ranibizumab (IVR);
Group 2 (RK): patients received intravitreal 0.5mg ranibizumab (IVR) along with off-label topical ketorolac eye drop ;
Group 3 (RV): patients received one session verteporfin followed by intravitreal on the same day (a minimum of 1 hour after the start of verteporfin PDT)
All patients received monthly intravitreal 0.5mg ranibizumab for 3 months, followed by monthly pro re nata IVR to treat any residual disease
Patients were evaluated on a monthly basis</td></tr>
</table>

Bibliographic reference	**Semeraro F, Russo A, Delcassi L, Romano M R, Rinaldi M, Chiosi F, and Costagliola C. 2015. "Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy". Retina 35:1547-54.**
Intervention	Patients received one session verteporfin followed by intravitreal
Comparator	Patients received intravitreal 0.5mg ranibizumab (IVR);
Outcomes	Mean change in VA Mean change in CRT The number of needed ranibizumab re-treatment over 12 month period Any adverse ocular reported at 12 months
Analyses	Descriptive statistics One way analysis of variance
Length of follow up	12 months
Results	

	PDT + ranibizumab	Ranibizumab (IVR) + off-label topical ketorolac eye drop	Ranibizumab	Effect between combined PDT+ranibizumab and ranibizumab (95%CI)
Number of patients	25	25	25	
VA, logMAR				
Baseline	0.59 (0.20)	0.60 (0.24)	0.61 (0.30)	-0.02 (-0.16, 0.12)
Month 2	0.44 (0.16)	0.33(0.17)	0.47 (0.28)	-0.03 (-0.16, 0.10)
Month 4	0.45 (0.16)	0.32 (0.15)	0.46 (0.31)	-0.01 (-0.15, 0.13)
Month 6	0.47 (0.18)	0.30 (0.21)	0.41 (0.28)	0.06 (-0.07, 0.19)
Month 8	0.46 (0.17)	0.30(0.19)	0.44 (0.25)	0.02 (-0.10, 0.14)
Month 10	0.48 (0.17)	0.33 (0.18)	0.45 (0.23)	0.03 (-0.08, 0.14)
Month12	0.49 (0.14)	0.34(0.17)24.5	0.48 (0.28)	0.01 (-0.11, 0.13)
CRT, um (SD)				

Bibliographic reference	Semeraro F, Russo A, Delcassi L, Romano M R, Rinaldi M, Chiosi F, and Costagliola C. 2015. "Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy". Retina 35:1547-54.

baseline	439 (74)	420(87)	440 (84)	-1.00 (-44.88, 42.88)
Month 2	313 (35)	318 (43)	339 (87)	-26.00 (-62.76, 10.76)
Month 4	301 (20)	305(45)	340 (52)	-39.00 (-60.84, -17.16)
Month 6	312 (37)	293 (54)	326 (47)	-14.00 (-37.45, 9.45)
Month 8	318 (36)	287 (46)	329 (43)	-11.00 (-32.98, 10.98)
Month 10	331 (39)	282 (46)	337 (46)	-6.00 (-29.64, 17.64)
Month 12	309 (17)	279 (50)	315(34)	
No. of ranibizumab treatment needed	5.8(1.3)	6.5 (1.2)	7.8 (1.0)	-2.00 (-2.64, -1.36)

No serious adverse effects were observed during the study period.

Missing data handling/loss to follow up	All patients completed the study
Was allocation adequately concealed?	Unclear (not details reported in the study)
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Sample within each group were small

Bibliographic reference	Semeraro F, Russo A, Delcassi L, Romano M R, Rinaldi M, Chiosi F, and Costagliola C. 2015. "Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy". Retina 35:1547-54.
Were incomplete outcome data adequately addressed?	N/A
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Vallance J H, Johnson B, Majid M A, Banerjee S, Mandal K, and Bailey C C. 2010. "A randomised prospective double-masked exploratory study comparing combination photodynamic treatment and intravitreal ranibizumab vs intravitreal ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Eye 24:1561-7.
Coutry/ies where the study carried out	UK
Study type	RCT
Aim of the study	The aim of this study is to evaluate the effect of standard-fluence verteporfin photodynamic therapy (PDT) delivered on the first day of a ranibizumab regimen for choroidal neovascularisation secondary to age-related macular degeneration compared with ranibizumab monotherapy.
Study dates	Not reported
Sources of funding	Not reported
Sample size	18
Inclusion Criteria	Patients have a BCVA logMAR visual acuity in the study eye between 24 and 73 letters Patients had a CNV of any type with the following characteristics as determined by fluorescein angiography: Evidence that CNV extends under the geometric centre of the foveal avascular zone CNV occupying liner dimension 5400um or less No subfoveal atrophic change and no subfoveal fibrosis and a total area of fibrosis 50% or less of total lesion area For occult with no classic CNV, the lesion must demonstrate presumed recent disease progression as assessed by the investigator and defined at least one the following criteria:

Bibliographic reference	Vallance J H, Johnson B, Majid M A, Banerjee S, Mandal K, and Bailey C C. 2010. "A randomised prospective double-masked exploratory study comparing combination photodynamic treatment and intravitreal ranibizumab vs intravitreal ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Eye 24:1561-7.
	• Blood associated with the lesion at baseline • 10% or more increase in GLD as assessed by FA in the past 3 months • Loss of visual acuity in the last 3 months defined as either 5 letter or more logMAR vision as determined by protocol refraction and protocol measurement or 2 lines or more using a Snellen chart by standard examination
Exclusion Criteria	Any previous CNV treatment in the study eye Treatment with verteporfin in the non-study eye less than 7 days preceding enrolment Any previous participation in a clinical trial involving anti-angiogenic drugs Previous intravitreal drug delivery in the study eye History of vitrectomy, glaucoma filtration surgery, corneal transplant or submacular surgery/other interventions for AMD in the study or any intraocular surgery in the study eye within 2 months of enrolment Greater than milder non-proliferative diabetic retinopathy or any diabetic maculopathy Previous retinal vascular occlusions Subretinal haemorrhage that involves the centre of the foveal, if the size of haemorrhage is either greater than 50% of the total lesion area or more than 1 disc area in size CNV in either eye due to cause other than AMD Retinal pigment epithelial tear involving the macular in the study eye Active intraocular inflammation, or a history of uveitis History of rhegmatogenous retinal detachment or macular hole (stage 3 or 4) in the study eye Infectious conjunctive, keratitis, scleritis, or endopthalmitis in either eye Aphakia or absence of the posterior capsule in the study eye, unless as a result of YAG posterior capsulotomy with previous posterior chamber intraocular lens implantation Spherical equivalent of the refractive error in the study eye of more than -8D of myopia or signs of pathologic myopia with a refraction of -4 to -8D. For patients who have undergone cataract surgery in the study eye, a preoperative myopic refractive error of more than -8D Uncontrolled glaucoma in the study eye, defined as intraocular pressure of greater than 30mmHg despite anti-glaucoma medication

<table>
<tr><th>Bibliographic reference</th><td>Vallance J H, Johnson B, Majid M A, Banerjee S, Mandal K, and Bailey C C. 2010. "A randomised prospective double-masked exploratory study comparing combination photodynamic treatment and intravitreal ranibizumab vs intravitreal ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Eye 24:1561-7.</td></tr>
<tr><td></td><td>Any concurrent intraocular condition in the study eye that, in the opinion of the investigator, is likely to require medical or surgical least 2 Snellen lines of BCVA over the study period
History of recent stroke or cardiac event, or uncontrolled angina or blood pressure</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Verteporfin PDT + ranibizumab</td><td>Sham PDT + ranibizumab</td></tr>
<tr><td>Number of patients</td><td>9</td><td>9</td></tr>
<tr><td>% of predominantly classic CNV</td><td>44.4</td><td>44.4</td></tr>
<tr><td>% of minimally classic CNV</td><td>55.6</td><td>55.6</td></tr>
<tr><td>Mean visual acuity, letter</td><td>50</td><td>55</td></tr>
<tr><td>Mean greatest linear dimension of lesion (microns)</td><td>3185</td><td>2569</td></tr>
<tr><td>Mean central retinal thickness (microns)</td><td>331</td><td>335</td></tr>
<tr><td>Mean reading speed (word per minute)</td><td>126</td><td>172</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were randomised to intravitreal injection of ranibizumab (0.5mg) and sham or standard-fluence verteporfin PDT at baseline (first visit)
All patients received a further 2 monthly ranibizumab treatment
Thereafter patients received monthly treatment with ranibizumab as required (if there was a loss of more than 5 letter of BCVA associated with intraretinal or subretinal fluid on OCT, or a more than 100um increase in the mean CRT when compared to the measurement obtained following 3 initial ranibizumab doses).
All patients underwent monthly visual acuity and OCT assessment and 3-monthly fluorescein angiography with follow-up to 1 year.</td></tr>
<tr><td>Intervention</td><td>Intravitreal injection of ranibizumab and standard-fluence verteporfin PDT</td></tr>
<tr><td>Comparator</td><td>Intravitreal injection of ranibizumab and sham verteporfin PDT</td></tr>
<tr><td>Outcomes</td><td>Best-corrected visual acuity</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Vallance J H, Johnson B, Majid M A, Banerjee S, Mandal K, and Bailey C C. 2010. "A randomised prospective double-masked exploratory study comparing combination photodynamic treatment and intravitreal ranibizumab vs intravitreal ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Eye 24:1561-7.</th></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Verteporfin PDT + ranibizumab</td><td>Sham PDT + ranibizumab</td><td>Effects (95%CI)</td></tr>
<tr><td>Number of patients</td><td>9</td><td>9</td><td></td></tr>
<tr><td>VA</td><td></td><td></td><td></td></tr>
<tr><td>Mean BCVA gain (range) at Month 12</td><td>2.2 (-8, +24)</td><td>4.4 (-11, +20)</td><td></td></tr>
<tr><td>Mean BCVA gain after initial 3 treatments</td><td>3.1 letters</td><td>6.5 letters</td><td></td></tr>
<tr><td>% of patients gaining ≥15 letters Month 12</td><td>11.1 (n=1)</td><td>11.1(n=1)</td><td>1.00 (0.07, 13.64)</td></tr>
<tr><td>% of patients gaining≥ 10 letters Month 12</td><td>11.1 (n=1)</td><td>33.3 (n=3)</td><td>0.33 (0.04, 2.63)</td></tr>
<tr><td>% of patients gaining <15 letters Month 12</td><td>100</td><td>100</td><td></td></tr>
<tr><td>% of patients gaining <10 letter Month 12</td><td>100 (n=9)</td><td>88.9 (n=8)</td><td>1.12 (0.83, 1.50)</td></tr>
<tr><td>CFT, µm</td><td></td><td></td><td></td></tr>
<tr><td>Mean reduction, at month 12</td><td>138</td><td>103</td><td></td></tr>
<tr><td>Mean reading speed at Month 12</td><td>136</td><td>171</td><td></td></tr>
<tr><td>Retreatment</td><td></td><td></td><td></td></tr>
<tr><td>Mean number (range) by Month 12</td><td>1.3 (0,3)</td><td>1.3 (0,3)</td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Vallance J H, Johnson B, Majid M A, Banerjee S, Mandal K, and Bailey C C. 2010. "A randomised prospective double-masked exploratory study comparing combination photodynamic treatment and intravitreal ranibizumab vs intravitreal ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Eye 24:1561-7.
	<table><tr><td>Mean number by Month 6</td><td>0.2</td><td>0.4</td><td></td></tr><tr><td>Mean time to first retreatment (months)</td><td>4.6</td><td>2.8</td><td></td></tr></table>
Missing data handling/loss to follow up	None
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Yes (assessors were blinded when assessing FA imaging)
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Small sample size
Were incomplete outcome data adequately addressed?	N/A
Are reports of the study free of suggestion of selective outcome reporting?	Yes

<table>
<tr><th>Bibliographic reference</th><th>Weingessel B ; Mihaltz K ; Vecsei-Marlovits P V. Predictors of 1-year visual outcome in OCT analysis comparing ranibizumab monotherapy versus combination therapy with PDT in exsudative age-related macular degeneration. The Central European Journal of Medicine128: 560-65. 2016.</th></tr>
<tr><td>Coutry/ies where the study carried out</td><td>Austria</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Aim of the study</td><td>The aim of this study was to find predictive factors of 1-year visual outcome, analyzing novel optical coherence tomography (OCT) biomarkers in exsudative age-related macular degeneration (choroidal neovascularization (CNV)) in two groups of different treatment modalities.</td></tr>
<tr><td>Study dates</td><td>Published 2016</td></tr>
<tr><td>Sources of funding</td><td>Not reported</td></tr>
<tr><td>Sample size</td><td>34</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients with a subfoveal CNV showing activity: presence of retinal haemorrhage, intraretinal oedema, subretinal fluid, or fibrovascular pigment epithelial detachment
Patients had visual acuity as their BCVA letter score 73-24 letters
Patietns had lesion size of ≤5400µm
Patients were willing to return for scheduled visits for 12-month period</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients with CNV which was not subfoveal or not related to AMD
Patients had received any prior treatment for AMD</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>PDT +ranibizumab</td><td>ranibizumab</td></tr>
<tr><td>Number of patients</td><td>14</td><td>16</td></tr>
<tr><td>Number of patients with classic lesion</td><td>18</td><td>14</td></tr>
<tr><td>Mean age, years</td><td>83.3 (6.1)</td><td>81.1 (7.9)</td></tr>
<tr><td>BCVA (ETDRS letters)</td><td>61.3 (12.0)</td><td>53.8 (11.4)</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Eligible patietns were randomised 1:1 to receive either ranibizumab monotherapy or ranibizumab combined with PDT with verteporfin.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Weingessel B ; Mihaltz K ; Vecsei-Marlovits P V. Predictors of 1-year visual outcome in OCT analysis comparing ranibizumab monotherapy versus combination therapy with PDT in exsudative age-related macular degeneration. The Central European Journal of Medicine128: 560-65. 2016.</td></tr>
<tr><td></td><td>Ranibizumab monotherapy: 0.5mg at month 0,1,2, from 3 to 12, ret-treatment with ranibizumab was performed if one of the following changes was observed between visists: new intra- or subretinal fluid, the macular as detected by OCT, an increase in OCT central retinal thickness of at least 100µm, or new macular haemorrhage.
Combined therapy: patients in the combination group received verteporfin PDT 1 day after the intravitreal injection 0.5mg of ranibizumab at baseline. At month 1 and 2, ranibizuman was injectioned without PDT; from month 3 to 12, the same rec-treatment criteroia for ranibizumab were used as in the monotherapy group.</td></tr>
<tr><td>Intervention</td><td>Ranibizumab injection combined with PDT</td></tr>
<tr><td>Comparator</td><td>Ranibizumab injections</td></tr>
<tr><td>Outcomes</td><td>Changes in visual acuity
Foveal thickness
Number of injections</td></tr>
<tr><td>Analyses</td><td>Two tailed paired t test</td></tr>
<tr><td>Length of follow up</td><td>12 month</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>PDT + ranibizumab</td><td>Ranibizumab</td><td>Effect (95%CI)</td></tr>
<tr><td>Number of patients</td><td>14</td><td>16</td><td></td></tr>
<tr><td>Visual acuity, ETDRS letters (SD)</td><td></td><td></td><td></td></tr>
<tr><td>3-month</td><td>62.6 (19.2)</td><td>57.3 (17.6)</td><td>5.3 (-7.95, 18.55)</td></tr>
<tr><td>6-month</td><td>62.4 (19.9)</td><td>57.8 (18.4)</td><td>4.6 (-9.18, 18.38)</td></tr>
<tr><td>12-month</td><td>57.2 (24.4)</td><td>58.7 (17.6)</td><td>-1.50 (-16.82, 13.92)</td></tr>
<tr><td>Number if intravitreal injections</td><td>6.9 (1.1)</td><td>7.4 (1.4)</td><td>-0.50 (-1.40, 0.40)</td></tr>
</table>
</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>30 of a total of 34 patient completed 12-month follow-up</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>Unclear</td></tr>
</table>

Bibliographic reference	Weingessel B ; Mihaltz K ; Vecsei-Marlovits P V. Predictors of 1-year visual outcome in OCT analysis comparing ranibizumab monotherapy versus combination therapy with PDT in exsudative age-related macular degeneration. The Central European Journal of Medicine128: 560-65. 2016.
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Relative small sample size in each group
Were incomplete outcome data adequately addressed?	Unclear
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	Williams P D, Callanan D, Solley W, Avery R L, Pieramici D J, and Aaberg T. 2012. "A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Clinical ophthalmology (Auckland, and N.Z.) 6:1519-25.
Coutry/ies where the study carried out	USA
Study type	RCT
Aim of the study	This prospective multi-centre pilot study compares the use of half-fluence photodynamic therapy combined with ranibizumab with ranibizumab monotherapy for the treatment of neovascular age-related macular degeneration.
Study dates	Not reported
Sources of funding	Novartis Pharmaceutics
Sample size	60

<table>
<tr><th>Bibliographic reference</th><td>Williams P D, Callanan D, Solley W, Avery R L, Pieramici D J, and Aaberg T. 2012. "A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Clinical ophthalmology (Auckland, and N.Z.) 6:1519-25.</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients with untreated subfoveal neovascular AMD</td></tr>
<tr><td>Exclusion Criteria</td><td>Patients with pigment epithelial detachments greater than 50% of the total lesion size</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>PDT +ranibizumab</td><td>ranibizumab</td></tr>
<tr><td>Number of patients</td><td>29</td><td>27</td></tr>
<tr><td>Number of patients with classic lesion</td><td>18</td><td>14</td></tr>
<tr><td>Mean age, years</td><td>79.3</td><td>79.1</td></tr>
</table>
</td></tr>
<tr><td>Study procedures</td><td>Patients were randomised to receive either 3 consecutive monthly ranibizumab injections or one ranibizumab injection combined with half-fluence PDT
Patients were monitored monthly for 12 months and re-treated PRN based on clinical discretion using standardised visual acuity testing (ETDR), clinical finings, and OCT
Patients in ranibizumab group were only re-treated with ranibizumab.
Patients in combined group were retreated with combined therapy as long as the patient had not received PDT within the previous 90 days. If the patient was within the 90 day post-PDT, the patient was only re-treated with ranibizumab.</td></tr>
<tr><td>Intervention</td><td>Ranibizumab injection combined with half-fluence PDT</td></tr>
<tr><td>Comparator</td><td>Ranibizumab injections</td></tr>
<tr><td>Outcomes</td><td>Changes in visual acuity
Foveal thickness
Number of injections</td></tr>
<tr><td>Analyses</td><td>Two tailed t test</td></tr>
<tr><td>Length of follow up</td><td>12 month</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>PDT + ranibizumab</td><td>Ranibizumab</td><td>Effect (95%CI)</td></tr>
<tr><td>Number of patients</td><td>29</td><td>27</td><td></td></tr>
<tr><td>Visual acuity, letters (range)</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Williams P D, Callanan D, Solley W, Avery R L, Pieramici D J, and Aaberg T. 2012. "A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Clinical ophthalmology (Auckland, and N.Z.) 6:1519-25.
	Baseline: 49.2 (5, 95); 52.9 (14, 93) Month 12: 51.8 (15, 82); 62.8 (20, 85) N (%) patients lost ≥15 letters: 4 (14); 6 (22); 0.62 (0.20, 1.96) N (%) patients gained ≥15 letters: 9 (31); 9 (33); 0.93 (0.44, 1.99) Central foveal thickness, um (range) Baseline: 320.5 (212, 538); 313.6 (151, 635) Month 12: 213.8; 221.1 (136, 275) Mean number of injections: 3.0; 6.8
Missing data handling/loss to follow up	56 of a total of 60 patient completed 12-month follow-up
Was allocation adequately concealed?	Unclear
Was knowledge of the allocated intervention adequately prevented during the study?	Unclear
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	Relative small sample size in each group
Were incomplete outcome data adequately addressed?	Unclear

Bibliographic reference	Williams P D, Callanan D, Solley W, Avery R L, Pieramici D J, and Aaberg T. 2012. "A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration". Clinical ophthalmology (Auckland, and N.Z.) 6:1519-25.
Are reports of the study free of suggestion of selective outcome reporting?	Yes