H.6.3 Adjunctive therapies

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

H.6.3.1 Anti-VEGF +PDT vs anti-VEGF

Anti-VEGF + PDR vs anti-VEGF BCVA (ETDRS letters ≤3 months) - positive values favour combination I (Lazic)* RCT Serious¹ Not serious Not serious Serious² 106 MD -7.25 (-19.82, 5.31) BCVA (ETDRS letters >3 months) - positive values favour combination I1 (Datseris; BCT Not serious³ Not serious Not serio	AIILI-VEOI ·I DI V	3 and VEO											
ACVA (ETDRS letters ≤3 months) - positive values favour combination 1 (Lazic)* RCT Serious¹ Not serious Not serious Serious² 106 MD -7.25 (-19.82, 5.31) 3 CVA (ETDRS letters >3 months) - positive values favour combination 11 (Datseris; Bashshur; Hatz; Kaiser; Krebs; Larsen; Semeraro*; Not serious Serious Not serious Positive values greater than 1 favour combination 3 CVA (proportion gain ≥15 letters, >3 months) - values greater than 1 favour combination 4 (Datseris; Bashshur; Hatz; (aiser; Larsen; Vallence; Williams; Gomi; Koh) 5 (Datseris; Bashshur; Hatz; (aiser); Larsen; Vallence; Williams; Gomi; Koh) 7 Color (Samonths) - positive values favour monotherapy 8 CT Serious⁴ Serious⁵ Not serious Not serious Not serious Not serious Not serious A88 MD -1.43 (-2.42, -0.45) 1 COW Bashshur; Larsen; Comi; Koh) 1 Cotal number of injections (>3 months) - positive values favour monotherapy	Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality				
If (Lazic)* RCT Serious¹ Not serious Not serious Serious² 106 MD -7.25 (-19.82, 5.31) BCVA (ETDRS letters >3 months) - positive values favour combination If (Datseris; Bashshur; Hatz; (aiser; Krebs; Larsen; Semeraro*; Weingessel; Williams: Gomi; Koh) BCVA (proportion gain ≥15 letters, >3 months) - values greater than 1 favour combination P (Datseris; Bashshur; Hatz; (aiser; Larsen; Vallance; Williams: Gomi; Koh) RCT Not serious Not serious Serious Serious² 923 RR 0.76 (0.63, 0.92) RCT Serious Foreius Foreius Not serious Not serious Not serious Serious² 923 RR 0.76 (0.63, 0.92) RCT Serious Foreius Fo	Anti-VEGF + PDR v	Anti-VEGF + PDR vs anti-VEGF											
(-19.82, 5.31) BCVA (ETDRS letters >3 months) - positive values favour combination 11 (Datseris; RCT Not serious Serious Serious Not serious Serious P23 RR 0.76 (0.63, 0.92) BCVA (proportion gain ≥15 letters, >3 months) - values greater than 1 favour combination D (Datseris; RCT Not serious Not serious Serious P23 RR 0.76 (0.63, 0.92) Callance; Williams: Somi; Koh) Reinjections (>3 months) - positive values favour monotherapy Serious Not	BCVA (ETDRS letters ≤3 months) - positive values favour combination												
11 (Datseris; Bashshur; Hatz; (aiser; Krebs; Larsen; Villiams: Gomi; Koh) RCT Not serious P23 RR 0.76 MODERATE Sashshur; Hatz; (aiser; Larsen; Villiams: Gomi; Koh) Reinjections (>3 months) - positive values favour monotherapy 5 (Datseris; Bashshur; Larsen; Comi; Koh) RCT Serious⁴ Serious⁵ Not serious	1 (Lazic)*	RCT	Serious ¹	Not serious	Not serious	Serious ²	106		LOW				
Bashshur; Hatz; Kaiser; Krebs; Larsen; Semeraro*; Weingessel; Williams: Gomi; Koh) BCVA (proportion gain ≥15 letters, >3 months) - values greater than 1 favour combination O (Datseris; Bashshur; Hatz; Kaiser; Larsen; Kaiser; Larsen; Gomi; Koh) Reinjections (>3 months) - positive values favour monotherapy 5 (Datseris; RCT Serious⁴ Serious⁵ Not serious Not serious Not serious Not serious Not serious Serious² Bashshur; Larsen; Gomi; Koh) Reinjections (>3 months) - positive values favour monotherapy Formal number of injections (>3 months) - positive values favour monotherapy Formal number of injections (>3 months) - positive values favour monotherapy	BCVA (ETDRS lette	rs >3 month	s) - positive valu	es favour combii	nation								
O (Datseris; RCT Not serious Not serious Serious ² 923 RR 0.76 (0.63, 0.92) Reinjections (>3 months) - positive values favour monotherapy O (Datseris; RCT Serious ⁴ Serious ⁵ Not serious Not se	11 (Datseris; Bashshur; Hatz; Kaiser; Krebs; Larsen; Semeraro*; Weingessel; Williams: Gomi; Koh)	RCT	Not serious ³	Not serious	Not serious	Not serious	1025		HIGH				
Sashshur; Hatz; Kaiser; Larsen; Vallance; Williams: Gomi; Koh) Reinjections (>3 months) - positive values favour monotherapy 5 (Datseris; RCT Serious ⁴ Serious ⁵ Not serious Not serious 488 MD -1.43 LOW Gashshur; Larsen; Gomi; Koh) Fotal number of injections (>3 months) - positive values favour monotherapy	BCVA (proportion g	jain ≥15 lette	ers, >3 months) -	values greater t	han 1 favour coml	oination							
Total number of injections (>3 months) - positive values favour monotherapy Not serious Not serious Not serious Not serious Not serious Not serious 488 MD -1.43 (-2.42, -0.45)	9 (Datseris; Bashshur; Hatz; Kaiser; Larsen; Vallance; Williams: Gomi; Koh)	RCT	Not serious ³	Not serious	Not serious	Serious ²	923		MODERATE				
Bashshur; Larsen; Gomi; Koh) Total number of injections (>3 months) - positive values favour monotherapy	Reinjections (>3 mo	onths) - posi	tive values favou	r monotherapy									
	5 (Datseris; Bashshur; Larsen; Gomi; Koh)	RCT	Serious ⁴	Serious ⁵	Not serious	Not serious	488		LOW				
G (Lim; Krebs; RCT Serious ⁴ Serious ⁵ Not serious Not serious 474 MD -0.94 LOW	Total number of injections (>3 months) - positive values favour monotherapy												
	6 (Lim; Krebs;	RCT	Serious ⁴	Serious ⁵	Not serious	Not serious	474	MD -0.94	LOW				

Number of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality		
Larsen; Semeraro; Weignessel, Williams)							(-1.76, -0.12)			
Proportion needing	Proportion needing retreatment (>3 months) - values greater than 1 favour combination									
1 (Hatz)	RCT	Serious ⁶	N/A	Not serious	Serious ²	40	RR 0.69 (0.42, 1.13)	LOW		
Proportion having of	Proportion having ocular adverse events - values greater than 1 favour combination									
5 (Lazic; Bashshur; Hatz; Kaiser; Larsen)	RCT	Not serious ³	Not serious	Not serious	Not serious	762	RR 1.03 (0.88, 1.21)	HIGH		
Proportion having non-ocular adverse events - values greater than 1 favour combination										
1 (Larsen)	RCT	Not serious	N/A	Not serious	Serious ²	255	RR 1.03 (0.82, 1.29)	MODERATE		

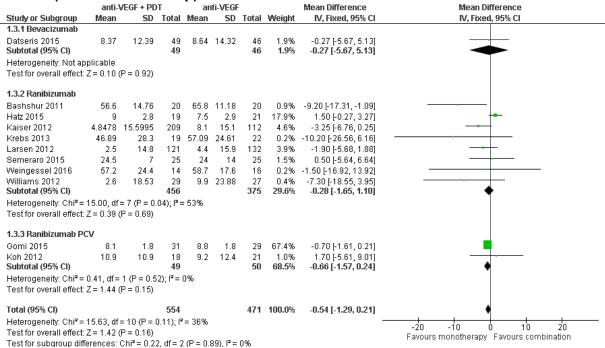
- 1. Downgraded one level for study design (open label, single blinded)
- 2. Downgraded one level for confidence interval crossing 1 line of a defined minimal important difference.
- 3. Some individual studies at high-risk of bias, but overall risk of bias rated low due to consistency of effect size estimates between high and low quality studies.
- 4. Downgraded one level for includes open label studies; lack of appropriate assessor masking.
- 5. Downgraded one level for heterogeneity (i²>50%).
- 6. Downgraded one level for selection bias (differences in baseline characteristics between treatment groups)

^{*}visual acuity outcome reported in the study used logMAR, and was converted to number of letters (logMAR=no. of letters × -0.02).

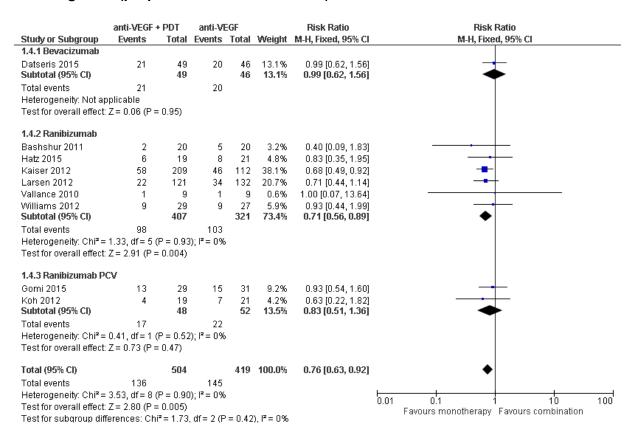
Meta-analysis: Anti-VEGF + PDT vs anti-VEGF

Visual acuity

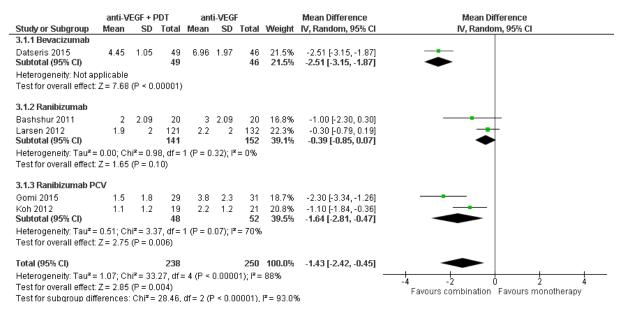
Letters (>3 month follow-up)



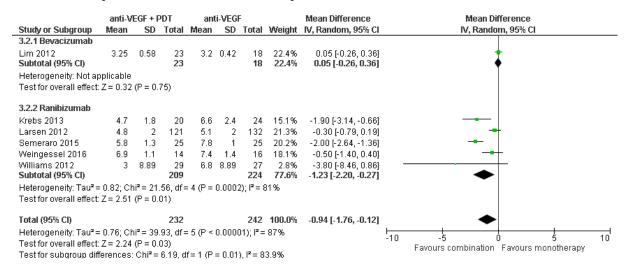
Letters gained (proportion 15 or more letters)



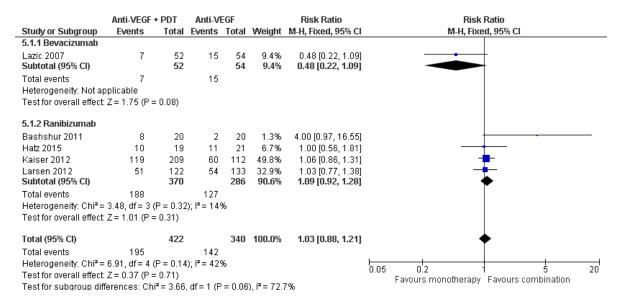
Number of injections: reinjections



Number of injections: total number of injections



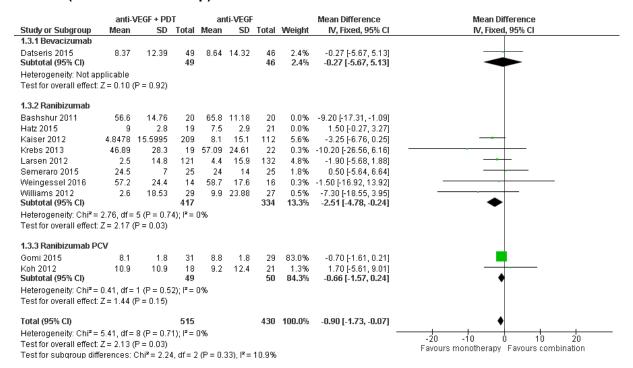
Ocular adverse events



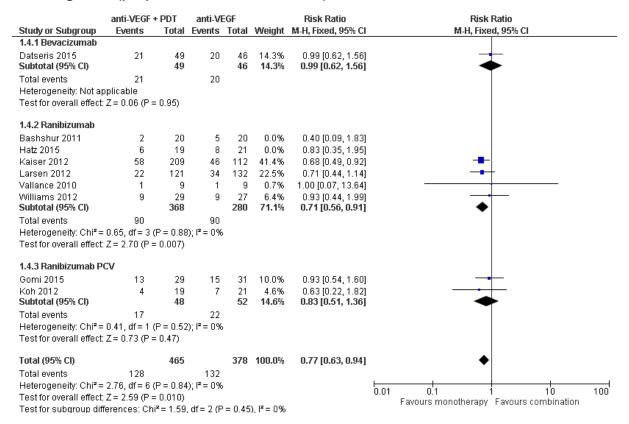
Meta-analysis (excluded study population with previous treatment history)

Visual acuity

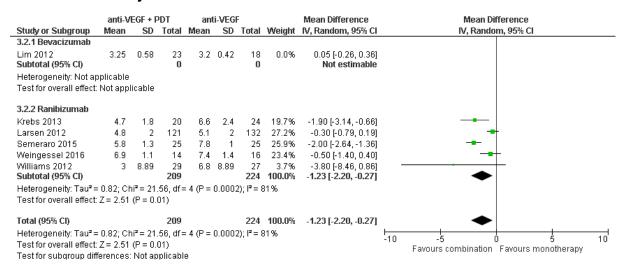
Letters (>3 month follow-up)



Letters gained (proportion 15 or more letters)



Total number of injections



Proportion of people had ocular adverse events

