H.6.1.10 Treatment frequency: PRN-and-extend vs PRN

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Gain of ≥15 letters at one year							
1 study (Eldem 2015)	Serious[1]	N/A	Not serious	Very serious[2]	67	RR 1.48 (0.72, 3.05)	VERY LOW
Mean change in BCVA in ETDRS letters at one year (higher scores indicate better vision)							
1 study (Elden 2015)	Serious[1]	N/A	Not serious	Serious[3]	67	MD 4.50 (-3.78, 12.78)	LOW

Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Mean number of injections at one year							
1 study (Eldem 2015)	Serious[1]	N/A	Not serious	Serious[4]	67	MD 1.1	LOW
Adverse events (serious systemic events at one year)							
1 study (Eldem 2015)	Serious[1]	N/A	Not serious	Very serious[2]	67	RR 1.71 (0.44, 6.66)	VERY LOW
Adverse events (ocular events at one year)							
1 study (Eldem 2015)	Serious[1]	N/A	Not serious	Very serious[2]	67	RR 0.99 (0.70, 1.38)	VERY LOW

1. Downgraded one level for risk of bias due to open label study design
2. Downgraded two levels of serious imprecision due to 95% confidence interval of estimated effect crossing 2 lines of a defined minimal important difference
3. Downgraded one level for imprecision due to 95% confidence interval of estimated effect crossing 1 line of defined minimal important difference
4. Downgraded one level for imprecision due to SD cannot be estimated to estmate confidence interval of the effect

Network meta-analysis on anti-angiogenic therapies and treatment frequency (network meta-analysis results are provided in Appendix G)

No. of studies	Study design	Sample size	Comparison	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean change in BCVA at 12 months								
26	RCT	10,925	Anti-VEGF agents vs placebo	Not serious	Not serious	Not serious	Not serious	HIGH
			Head-to-head anti-VEGF agents	Not serious	Not serious	Not serious	Not serious	HIGH
			Photodynamic therapy compared with placebo	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy	Not serious	Not serious	Not serious	Not serious	HIGH

No. of studies	Study design	Sample size	Comparison	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			compared with anti-VEGF					
			Anti-VEGF frequency – PRN compared with routine injection	Serious[2]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – PRN with and without loading phase	Serious[3]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – different frequencies of routine treatment	Serious[4]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – treat-and-extend compared with routine or PRN	Serious[2]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – PRN-and-extend compared with routine or PRN	Serious[3]	Not serious	Not serious	Serious[1]	LOW
Mean change in BCVA at 24 months								
12	RCT	7,623	Anti-VEGF agents vs placebo	Not serious	Not serious	Not serious	Not serious	HIGH
			Head-to-head anti-VEGF agents	Not serious	Not serious	Not serious	Not serious	HIGH
			Photodynamic therapy compared with placebo	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy compared with anti-VEGF	Not serious	Not serious	Not serious	Not serious	HIGH
			Anti-VEGF frequency – PRN compared with monthly	Not serious	Serious[6]	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – PRN with and without	Serious[3]	Not serious	Not serious	Not serious	MODERATE

No. of studies	Study design	Sample size	Comparison	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			loading phase					
			Anti-VEGF frequency – treat-and-extend compared with routine or PRN	Serious[2]	Not serious	Not serious	Serious[1]	LOW
Categorical change in BCVA[7] (change in ETDRS letters) at 12months								
24	RCT	9,950	Anti-VEGF agents vs placebo	Not serious	Not serious	Not serious	Not serious	HIGH
			Head-to-head anti-VEGF agents	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy compared with placebo	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy compared with anti-VEGF	Not serious	Not serious	Not serious	Not serious	HIGH
			Anti-VEGF frequency – PRN compared with routine treatment	Serious[3]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – PRN with and without loading phase	Serious[3]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – different frequencies of routine treatment	Serious[4]	Not serious	Not serious	Not serious	MODERATE
			Anti-VEGF frequency – treat-and-extend compared with routine or PRN	Serious[2]	Not serious	Not serious	Serious[1]	LOW
			Anti-VEGF frequency – PRN-and-extend compared with routine or PRN	Serious[3]	Not serious	Not serious	Serious[1]	LOW

[7] The estimated effects=z score * 13.7 (standard deviation) at 12 months; and z score *15.1(standard deviation) at 24 months

No. of studies	Study design	Sample size	Comparison	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Categorical change in BCVA (change in ETDRS letters) at 24 months								
10	RCT	7,041	Anti-VEGF agents vs placebo	Not serious	Not serious	Not serious	Not serious	HIGH
			Head-to-head anti-VEGF agents	Not serious	Not serious	Not serious	Not serious	HIGH
			Photodynamic therapy compared with placebo	Not serious	Not serious	Not serious	Serious[1]	MODERATE
			Photodynamic therapy compared with anti-VEGF	Not serious	Not serious	Not serious	Not serious	HIGH
			Anti-VEGF frequency – PRN compared with monthly	Not serious	Serious[6]	Not serious	Not serious	MODEATE
			Anti-VEGF frequency – PRN with and without loading phase	Serious[3]	Not serious	Not serious	Not serious	MODERATE

1. Downgraded one level due to confidence/credible intervals of estimated effects of comparison crossing 1 line of defined minimal important difference.
2. Downgraded one level for individual studies at risk of bias (treatment frequency/schedule were not masked to patients).
3. Downgraded one level for individual studies at risk of bias (randomisation, allocation concealment, and selective outcome reporting were unclear)
4. Downgraded one level of individual studies at risk of bias (study design, randomisation of the study).
5. Downgraded one level of individual studies at risk bias (treatment frequency/schedule were not masked to patients, study design or incomplete data)
6. Downgraded one level due to substantial inconsistency between study heterogeneity (i^2>50%)