**eTable 2.** Characteristics of the Individual Studies of Patients with nAMD Included in This Systematic Review

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study\*** | **Country** | **Group** | **n†** | **Duration** | **BCVA Outcomes** | **Treatment Interval** | | | **Number of Injections / Clinic Visits** |
| **RCTs (8 studies)** | | | | | | | | | |
| CANTREAT; Kertes et al 201930/202026 | Canada | Ranibizumab T&E | 287 | 24 months | Mean ± SD change from BL to Month 24: +6.8 ± 14.1 ETDRS letters | | Mean ± SD interval extension at Month 12: 8.7 ± 2.8 weeks; proportion of patients treated at ≥8-week intervals at Month 24: 73.7%, or a 12-week interval at Month 24: 43.1% | Mean injections from BL to Month 12: 9.4; over 24 months: 17.6 | |
| Ranibizumab monthly | 293 | 24 months | Mean ± SD change from BL to Month 24: +6.0 ± 12.6 ETDRS letters | | NA | Mean injections from BL to Month 12: 11.8; over 24 months: 23.5 | |
| TREND; Silva et al 201827 | 18 countries‡ | Ranibizumab T&E | 323 | 12 months | LS mean change from BL: +6.2 ETDRS letters | | Proportion of patients treated at ≥8-week intervals at Month 12: 61.9%, or a 12-week interval at Month 12: 18.6% | Mean ± SD injections: 8.7 ± 2.68 | |
| Ranibizumab monthly | 327 | 12 months | LS mean change from BL: +8.1 ETDRS letters | | NA | Mean ± SD injections: 11.1 ± 2.43 | |
| In-Eye; López Gálvez et al 202033 | Spain | Ranibizumab PRN | 104 | 12 months | Mean (95% CI) change from BL at Month 12:  ITT: +7.3 (4.3, 10.3) and PP: +8.0 (5.1, 11.0) | | NR | Mean (95% CI) injections: 7.4 (6.7, 8.0); mean (95% CI) visits: 13.6 (13.4, 13.7) | |
| Ranibizumab T&E | 99 | 12 months | Mean (95% CI) change from BL at Month 12:  ITT: +6.7 (3.7, 9.6) and PP: +6.4 (2.9, 9.8) | | NR | Mean (95% CI) injections: 9.3 (8.9, 9.7); mean (95% CI) visits: 10.4 (10.0, 10.8) | |
| Ranibizumab bimonthly | 102 | 12 months | Mean (95% CI) change from BL at Month 12:  ITT: +7.0 (4.0, 10.0) and PP: +7.2 (4.2, 10.2) | | NR | Mean (95% CI) injections: 7.6 (7.5, 7.7); mean (95% CI) visits: 8.6 (8.5, 8.7) | |
| ALTAIR; Ohji et al 2020a20 | Japan | Aflibercept T&E  (2-week)§ | 124 | 96 weeks | Mean (95% CI) change from BL at Week 96: 7.6 (5.0, 10.3) ETDRS letters | | Mean ± SD last treatment interval at Week 96: 12.2 ± 3.6 weeks; proportion of patients treated at ≥12-week intervals at Week 96: 56.9%, or a 16-week interval at Week 96: 41.5% | Mean ± SD injections from BL to Week 52: 7.2 ± 0.9; from Weeks 54 to 96: 3.6 ± 1.6; from BL to Week 96: 10.4 ± 2.6 | |
| Aflibercept T&E  (4-week)§ | 123 | 96 weeks | Mean (95% CI) change from BL at Week 96: 6.1 (3.1, 9.0) ETDRS letters | | Mean ± SD last treatment interval at Week 96: 12.5 ± 3.6 weeks; proportion of patients treated at ≥12-week intervals at Week 96: 60.2%, or a 16-week interval at Week 96: 46.3% | Mean ± SD injections from BL to Week 52: 6.9 ± 1.0; from Weeks 54 to 96: 3.7 ± 1.4; from BL to Week 96: 10.4 ± 2.4 | |
| ARIES; Mitchell et al 201931 | NR | Aflibercept early-start T&E¶ | 135 | 12 months | Absolute BCVA at Week 52: 67.6 ETDRS letters; change from randomization: +0.9 ETDRS letters | | NR | Mean injections: 7.2 | |
| Aflibercept late-start T&E¶ | 136 | 12 months | Absolute BCVA at Week 52: 68.3 ETDRS letters; change from randomization: +1.1 ETDRS letters | | NR | Mean injections: 8.0 | |
| FLUID; Guymer et al 201923 | Australia | Ranibizumab T&E (intensive retinal fluid treatment) | 174 | 24 months | Mean ± SD change from BL at Month 24: +3.0 ± 16.3 ETDRS letters | | Proportion of patients treated at a 12-week interval at Month 24: 15.0% | Mean ± SD injections from BL to Month 12: 9.5 ± 2.60; from Months 12 to 24: 8.4 ± 3.64 | |
| Ranibizumab T&E (relaxed retinal fluid treatment) | 175 | 24 months | Mean ± SD change from BL at Month 24: +2.6 ± 16.3 ETDRS letters | | Proportion of patients treated at a 12-week interval at Month 24: 29.6% | Mean ± SD injections from BL to Month 12: 8.9 ± 2.25; from Months 12 to 24: 7.6 ± 3.62 | |
| LUCAS; Berg et al 201549/201644 | Norway | Ranibizumab T&E | 218 | 24 months | Mean ± SD change from BL at Month 24 (PP analysis): +6.6 ± 15.2 ETDRS letters | | Mean treatment interval at Month 24: 7.6 weeks; proportion of patients treated at a 12-week interval at Month 24: 17% | Mean ± SD injections from BL to Month 12: 8.9 ± 2.6; from Months 12 to 24: 8.0 ± 3.6; over 24 months: 16.0 ± 5.5 | |
| Bevacizumab T&E | 213 | 24 months | Mean ± SD change from BL at Month 24 (PP analysis): +7.4 ± 16.0 ETDRS letters | | Mean treatment interval at Month 24: 6.5 weeks; proportion of patients treated at a 12-week interval at Month 24: 10% | Mean ± SD injections from BL to Month 12: 8.0 ± 2.3; from Months 12 to 24: 9.2 ± 3.5; over 24 months: 18.2 ± 5.6 | |
| RIVAL; Gillies et al 201950/202045 | Australia | Ranibizumab T&E | 142 | 24 months | Mean ± SD change from BL at Month 24: +6.5 ± 14.4 logMAR letters | | Proportion of patients treated at a 12-week interval at Month 24: 32% | Mean ± SD injections from BL to Month 12: 9.7 ± 2.77; from Months 12 to 24: 8.9 ± 3.2; over 24 months: 17.7 ± 6.4 | |
| Aflibercept T&E | 139 | 24 months | Mean ± SD change from BL at Month 24: +5.3 ± 13.3 logMAR letters | | Proportion of patients treated at a 12-week interval at Month 24: 31% | Mean ± SD injections from BL to Month 12: 9.7 ± 2.55; from Months 12 to 24: 8.3 ± 3.6; over 24 months: 17.0 ± 6.3 | |
| **Observational studies (14 studies)**  *11 retrospective observational studies, 2 unspecified observational studies, and 1 comparison of an RCT with an observational study* | | | | | | | | | |
| Almuhtaseb et al 2018; retrospective32 | UK | Aflibercept every 8 weeks | 51 eyes | 12 months | Mean change from BL at Month 12: +7.5 ETDRS letters | | NR | Mean injections: 7.00 | |
| Ranibizumab T&E | 49 eyes | 12 months | Mean change from BL at Month 12: +8.3 ETDRS letters | | NR | Mean injections: 7.75 | |
| Augsburger et al 2019; retrospective42 | Switzerland | Ranibizumab PRN | 722 eyes | Mean ± SD: 13.5 ± 16.2 months | n (%) patients who worsened, were unchanged, or improved based on change in BCVA (logMAR) from Day 1 to <2 months: 25 (4.6) / 385 (70.4) / 137 (25.0) | | NR | Mean ± SD injections: 6.3 ± 6.1; mean ± SD visits: 11.1 ± 14.6 | |
| Ranibizumab T&E | 191 eyes | Mean ± SD: 15.7 ± 14.6 months | n (%) patients who worsened, were unchanged, or improved based on change in BCVA (logMAR) from Day 1 to <2 months: 5 (3.0) / 114 (68.7) / 47 (28.3) | | NR | Mean ± SD injections: 9.4 ± 7.3 | |
| Aflibercept T&E | 419 | Mean ± SD: 15.6 ± 13.1 months | n (%) patients who worsened, were unchanged, or improved based on change in BCVA (logMAR) from Day 1 to <2 months: 11 (3.0) / 258 (70.3) / 98 (26.7) | | NR | Mean ± SD injections: 10.3 ± 8.1 | |
| Aurell et al 2019; retrospective43 | Sweden | Anti-VEGF PRN | 223 eyes | 12 months | Mean ± SD change from BL at Month 12: +1.2 ± 12.7 ETDRS letters | | NR | Mean ± SD injections: 6.3 ± 2.1 | |
| Anti-VEGF T&E | 220 eyes | 12 months | Mean ± SD change from BL at Month 12: +5.2 ± 11.8 ETDRS letters | | Mean ± SD interval at Month 12: 6.7 ± 2.8 weeks | Mean ± SD injections: 10.2 ± 2.1 | |
| Delaunay et al 201951 | NR | Ranibizumab T&E | 32 eyes | Mean follow-up time: 6.65 years | Mean BCVA at BL: 66.6 ETDRS letters; mean BCVA at Year 1: 74.1 ETDRS letters; mean BCVA at Year 2: 76.2 ETDRS letters | | Mean interval between treatments at the last review: 6.2 weeks | Mean injections per year over full follow-up: 8.6 | |
| Anti-VEGF non-T&E protocols | 225 eyes | Mean follow-up time: 6.53 years | Mean BCVA at BL: 59.7 ETDRS letters; mean BCVA at Year 1: 63.5 ETDRS letters; mean BCVA at Year 2: 63.2 ETDRS letters | | Mean interval between treatments at the last review: 10.5 weeks | Mean injections per year over full follow-up: 4.8 | |
| Garweg et al 2017a retrospective41 | Switzerland | Ranibizumab PRN | 68 eyes | Mean ± SD: 16.9 ± 5.6 months | Mean ± SD change from BL at Month 12: +0.66 ± 19.53 ETDRS letters | | NR | Mean ± SD injections from BL to Month 12: 5.5 ± 2.0 | |
| Ranibizumab T&E | 39 eyes | Mean ± SD: 21.8 ± 5.0 months | Mean ± SD change from BL at Month 12: +2.65 ± 16.60 ETDRS letters | | NR | Mean ± SD injections from BL to Month 12: 6.8 ± 2.4 | |
| Hatz et al 2017; retrospective case series24 | Switzerland | Ranibizumab PRN | 70 eyes | 12 months | Mean ± SD change from BL at Month 12: +0.07 ± 0.22 logMAR | | NR | Mean ± SD injections: 6.0 ± 1.9; mean ± SD visits: 11.9 ± 1.1 | |
| Ranibizumab T&E | 70 eyes | 12 months | Mean ± SD change from BL at Month 12: +0.18 ± 0.17 logMAR | | Mean ± SD max. period of extension without recurrence at Month 12: 8.9 ± 3.0 weeks | Mean ± SD injections:  8.6 ± 1.9 | |
| Jaki Mekjavić et al 2018; retrospective37 | Slovenia | Aflibercept T&E | 115 eyes | 24 months | Mean (95% CI) change from BL at Month 24: +7.0 (4.7, 9.3) ETDRS letters | | NR | Mean ± SD injections from BL to Month 12: 8.4 ± 1.9; mean ± SD visits from BL to Month 12: 8.8 ± 1.7; mean ± SD injections from Months 12 to 24: 6.1 ± 2.0; mean ± SD visits from Months 12 to 24: 6.4 ± 1.9 | |
| Aflibercept T&E and then PRN | 33 eyes | 24 months | Mean (95% CI) change from BL at Month 24: +1.2 (−3.1, 5.6) ETDRS letters | | NR | Mean ± SD injections from BL to Month 12: 7.8 ± 1.4; mean ± SD visits from BL to Month 12: 8.1 ± 1.4; mean ± SD injections from Months 12 to 24: 2.5 ± 1.7; mean ± SD visits from Months 12 to 24: 6.2 ± 1.8 | |
| Johnston et al2017; retrospective40 | Australia; UK | Ranibizumab T&E | 647 eyes | 12 months | Mean ± SE change from BL at Month 12: 5.00 ± 0.54 ETDRS letters | | NR | Mean ± SD injections: 9.29 ± 2.43; mean ± SD visits: 10.29 ± 2.90 | |
| Ranibizumab PRN | 3,187 eyes | 12 months | Mean ± SE change from BL at Month 12: 3.04 ± 0.24 ETDRS letters | | NR | Mean ± SD injections: 6.04 ± 2.19; mean ± SD visits: 11.47 ± 2.93 | |
| Mahmood et al 2018; retrospective93 | NR | Aflibercept stop | 640|| | 1 year | Mean change from BL at Month 12: +5.3 ETDRS letters; mean change from BL at Month 32: +3.7 ETDRS letters | | NR | Mean injections in Year 1: 6.8; in Year 2: 4.6; in Year 3: 4.3 | |
| Aflibercept T&E | 3 years |
| Aflibercept bimonthly |
| Aflibercept treatment intensified |
| Spooner et al 2020; retrospective MANEX study38,39 | Australia; Italy | Anti-VEGF T&E\*\* | 163 eyes | 4 years | Mean ± SD change from BL at Year 4: +0.56 ± 13.81 ETDRS letters | | NR | Mean ± SD injections over 4 years: 33.1 ± 9.5 | |
| Anti-VEGF PRN\*\* | 101 eyes | 4 years | Mean ± SD change from BL at Year 4: −3.94 ± 18.48 ETDRS letters | | NR | Mean ± SD injections over 4 years: 17.46 ± 6.15 | |
| Hamoud et al 202036 | UK | Ranibizumab PRN | 161 eyes | 12 months | Mean change from BL at Month 12: +2.08 ETDRS letters | | NR | Mean injections: 5.85 | |
| Ranibizumab T&E | 32 eyes | 12 months | Mean change from BL at Month 12: +7.10 ETDRS letters | | NR | Mean injections: 7.34 | |
| Aflibercept bimonthly | 111 eyes | 12 months | Mean change from BL at Month 12: +4.46 ETDRS letters | | NR | Mean injections: 6.97 | |
| Abdin et al 2019; retrospective46 | Germany | Ranibizumab T&E | 50 eyes | 12 months | Mean ± SD change from BL at Month 12: +3.2 ± 9.0 ETDRS letters | | Mean ± SD max. visit-free interval: 64 ± 15 days | Mean ± SD injections per eye after loading phase: 5.8 ± 1.4 | |
| Aflibercept T&E | 50 eyes | 12 months | Mean ± SD change from BL at Month 12: +1.4 ± 9.4 ETDRS letters | | Mean ± SD max. visit-free interval: 67 ± 19 days | Mean ± SD injections per eye after loading phase: 6.1 ± 1.3 | |
| Garweg et al 2017b; retrospective case series47 | Switzerland | Aflibercept T&E | 106 eyes | 24 months | Mean change from BL at Month 3: +4.8 ETDRS letters; mean change from Months 3 to 24: −4.2 ETDRS letters | | NR | Mean ± SD injections from BL to Month 12: 7.5 ± 1.8; from Months 12 to 24: 4.3 ± 2.4 | |
| Ranibizumab T&E | 47 eyes | 24 months | Mean change from BL at Month 3: +5.8 ETDRS letters; mean change from Months 3 to 24: −4.5 ETDRS letters | | NR | Mean ± SD injections from BL to Month 12: 6.9 ± 2.2; from Months 12 to 24: 3.4 ± 2.5 | |
| Mitchell et al 2017; comparison of data from the TREND clinical trial and the LUMINOUS observational study94 | Australia | Ranibizumab T&E (TREND) | 323 | 12 months | Mean change from BL at Month 12: +6.6 ETDRS letters | | NR | Mean injections: 8.7 | |
| Ranibizumab routine clinical practice (“mostly T&E”; LUMINOUS) | 227 | 12 months | Mean change from BL at Month 12: +5.3 ETDRS letters | | NR | Mean injections: 7.9 | |
| **Meta-analyses (5 studies)** | | | | | | | | | |
| Kim et al 201634 | NA | Ranibizumab PRN | 21,612 | ≥1 year | Mean (95% CI) change from BL at Year 1: +3.5 (2.0, 5.0) ETDRS letters; from BL at Year 2: +1.3 (−1.6, 4.2) ETDRS letters | | NR | Mean (95% CI) yearly injections: 4.7 (4.0, 5.5); mean (95% CI) yearly visits: 8.8 (7.4, 10.3) | |
| Ranibizumab T&E | 2,566 | ≥1 year | Mean (95% CI) change from BL at Year 1: +8.8 (5.8, 11.8) ETDRS letters; from BL at Year 2: +6.7 (3.2, 10.1) ETDRS letters | | NR | Mean (95% CI) yearly injections: 6.9 (5.6, 8.2); mean (95% CI) yearly visits: 7.6 (5.9, 9.3) | |
| Li et al 2020 AMD study95 | NA | Anti-VEGF PRN | NR | ≥1 year | Mean difference (95% CI) in change from BL at Year 1, PRN vs monthly: −1.68 (−2.81, −0.55) ETDRS letters; mean difference (95% CI) in change from BL at Year 2, PRN vs monthly: −2.23 (−3.93, −0.53) ETDRS letters | | NR | Median injections at Year 1: 7.5 | |
| Anti-VEGF T&E | NR | ≥1 year | Mean difference (95% CI) in change from BL at Year 1, T&E vs monthly: +0.51 (−3.14, 4.16) ETDRS letters; mean difference (95% CI) in change from BL at Year 2, T&E vs monthly: +0.80 (−1.38, 2.98) ETDRS letters | | NR | Median injections at Year 1: 9.4 | |
| Ohji et al 2020b AMD study48 | NA | Aflibercept T&E | NR | 2 years | At Year 2, median difference (95% CrI) between aflibercept T&E and ranibizumab T&E regarding the numbers of ETDRS letters gained was not significant (Model 1: −2.29 [−8.10, 3.58]; Model 2: −0.55 [−6.34, 5.29]) | | NR | Aflibercept T&E was associated with significantly fewer injections compared with ranibizumab T&E (Model 1: −6.12 [−7.60, −4.65]; Model 2: −5.93 [−7.42, −4.45]) | |
| Ranibizumab T&E | NR | 2 years | NR |
| Okada et al 2018 AMD study35 | NA | Ranibizumab T&E | NR | ≥1 year | Mean difference (95% CI) in improvement of BCVA at Year 1, T&E vs monthly: −1.79 (−3.70, 0.13) ETDRS letters, and T&E vs PRN: +6.18 (3.28, 9.08) ETDRS letters | | NR | At Year 1, mean (95% CI) injections, T&E vs monthly: −1.6 (−3.0, −0.2), and T&E vs PRN: 1.44 (1.15, 1.73) | |
| Ranibizumab monthly | NR | ≥1 year | NR |
| Ranibizumab PRN | NR | ≥1 year | NR |
| Ye et al 2020 AMD study96 | NA | Ranibizumab T&E | NR | ≥1 year | Odds ratio (95% CrI) for proportion of patients gaining ≥15 ETDRS letters: ranibizumab T&E vs brolucizumab quarterly: 1.00 (0.59, 1.69); ranibizumab T&E vs bevacizumab T&E: 1.08 (0.67, 1.73) | | NR | NR | |
| Bevacizumab T&E | NR | ≥1 year | NR | NR | |
| Aflibercept T&E | NR | ≥1 year | NR | NR | |

\*Study name (if applicable), first author, and year of publication.

†Number of subjects receiving treatment in each comparison group.

‡Belgium, Croatia, Denmark, Egypt, Germany, Hungary, India, Israel, Italy, Korea, Portugal, Russia, Slovakia, Slovenia, Spain, Switzerland, Turkey, UK.

§The aflibercept T&E 2-week and 4-week adjustment groups included 46 and 44 patients diagnosed with PCV, respectively.

¶In the early-start T&E group, the T&E regimen was extended by 2 weeks or an initial 4-week interval to a maximum of 16 weeks. In the late-start T&E group, 2 mg of aflibercept was administered every 8 weeks until Week 52, followed by T&E.

||640 patients were included in the full cohort; the number of patients, mean change in BCVA from BL, and mean number of injections received were not separated by treatment group in this study.

\*\*The anti-VEGF T&E and PRN groups included 9 and 16 patients diagnosed with PCV, respectively.

AMD indicates age-related macular degeneration; BCVA, best-corrected visual acuity; BL, baseline; CI, confidence interval; CrI, credible interval; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intention-to-treat population; logMAR, logarithm of the minimum angle of resolution; LS, least squares; max., maximum; NA, not applicable; nAMD, neovascular age-related macular degeneration; NR, not recorded; PCV, polypoidal choroidal vasculopathy; PP, per-protocol population; PRN, pro re nata(as needed); RCT, randomized controlled trial; SD, standard deviation; SE, standard error; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.