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Treatment regimens for administration of anti-vascular endothelial growth factor agents for neovascular age-related macular degeneration (Review)

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[Intervention Review]

Treatment regimens for administration of anti-vascular endothelial growth factor agents for neovascular age-related macular degeneration

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A B S T R A C T

Background

Age-related macular degeneration (AMD) is one of the leading causes of permanent blindness worldwide. The current mainstay of treatment for neovascular AMD (nAMD) is intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents: aflibercept, ranibizumab, and off-label bevacizumab. Injections can be given monthly, every two or three months ('extended-fixed'), or as needed (pro re nata (PRN)). A variant of PRN is 'treat-and-extend' whereby injections are resumed if recurrence is detected and then delivered with increasing intervals. Currently, injection frequency varies among practitioners, which underscores the need to characterize an optimized approach to nAMD management.

Objectives

To investigate the effects of monthly versus non-monthly intravitreous injection of an anti-VEGF agent in people with newly diagnosed nAMD.

Search methods

We searched CENTRAL, MEDLINE, Embase, LILACS, and three trials registers from 2004 to October 2019; checked references; handsearched conference abstracts; and contacted pharmaceutical companies to identify additional studies.

Selection criteria

We included randomized controlled trials (RCTs) that compared different treatment regimens for anti-VEGF agents in people with newly diagnosed nAMD. We considered standard doses only (ranibizumab 0.5 mg, bevacizumab 1.25 mg, aflibercept 2.0 mg, or a combination of these).

Data collection and analysis

We used standard Cochrane methods for trial selection, data extraction, and analysis.

Main results

We included 15 RCTs. The total number of participants was 7732, ranging from 37 to 2457 in each trial. The trials were conducted worldwide. Of these, six trials exclusively took place in the US, and three included centers from more than one country. Eight trials were at high risk of bias for at least one domain and all trials had at least one domain at unclear risk of bias.

Seven trials (3525 participants) compared a PRN regimen with a monthly injection regimen, of which five trials delivered four to eight injections using standard PRN and three delivered nine or 10 injections using a treat-and-extend regimen in the first year. The overall mean change in best-corrected visual acuity (BCVA) at one year was +8.8 letters in the monthly injection group. Compared to the monthly injection, there was moderate-certainty evidence that the mean difference (MD) in BCVA change at one year for the standard PRN subgroup was –1.7 letters (95% confidence interval (CI) –2.8 to –0.6; 4 trials, 2299 participants), favoring monthly injections. There was low-certainty evidence of a similar BCVA change with the treat-and-extend subgroup (0.5 letters, 95% CI –3.1 to 4.2; 3 trials, 1226 participants).

Compared to monthly injection, there was low-certainty evidence that fewer participants gained 15 or more lines of vision with standard PRN treatment at one year (risk ratio (RR) 0.87, 95% CI 0.76 to 0.99; 4 trials, 2299 participants) and low-certainty evidence of a similar gain with treat-and-extend versus monthly regimens (RR 1.11, 95% CI 0.91 to 1.36; 3 trials, 1169 participants).

The mean change in central retinal thickness was a decrease of –166 μm in the monthly injection group; the MD compared with standard PRN was 21 μm (95% CI 6 to 32; 4 trials, 2215 participants; moderate-certainty evidence) and with treat-and extend was 22 μm (95% CI 37 to –81 μm; 2 trials, 635 participants; low-certainty evidence), in favor of monthly injection. Only one trial (498 participants) measured quality of life and reported no evidence of a difference between regimens, but data could not be extracted (low-certainty evidence).

Both PRN regimens (standard and 'treat-and-extend') used fewer injections than monthly regimens (standard PRN: MD –4.6 injections, 95% CI –5.4 to –3.8; 4 trials, 2336 participants; treat-and-extend: –2.4 injections, 95% CI –2.7 to –2.1 injections; moderate-certainty evidence for both comparisons). Two trials provided cost data (1105 participants, trials conducted in the US and the UK). They found that cost differences between regimens were reduced if bevacizumab rather than aflibercept or ranibizumab were used, since bevacizumab was less costly (low-certainty evidence).

PRN regimens were associated with a reduced risk of endophthalmitis compared with monthly injections (Peto odds ratio (OR) 0.13, 95% CI 0.04 to 0.46; 6 RCTs, 3175 participants; moderate-certainty evidence). Using data from all trials included in this review, we estimated the risk of endophthalmitis with monthly injections to be 8 in every 1000 people per year. The corresponding risk for people receiving PRN regimens was 1 in every 1000 people per year (95% CI 0 to 4).

Three trials (1439 participants) compared an extended-fixed regimen (number of injections reported in only one large trial: 7.5 in one year) with monthly injections. There was moderate-certainty evidence that BCVA at one year was similar for extended-fixed and monthly injections (MD in BCVA change compared to extended-fixed group: –1.3 letters, 95% CI –3.9 to 1.3; RR of gaining 15 letters or more: 0.94, 95% CI 0.80 to 1.10). The change in central retinal thickness was a decrease of 137 μm in the monthly group; the MD with the extended-fixed group was 8 μm (95% CI –11 to 27; low-certainty evidence). The frequency of endophthalmitis was lower in the extended-fixed regimen compared to the monthly group, but this estimate was imprecise (RR 0.19, 95% CI 0.03 to 1.11; low-certainty evidence). If we assumed a risk of 8 cases of endophthalmitis in 1000 people receiving monthly injections over one year, then the corresponding risk with extended-fixed regimen was 2 in 1000 people (95% CI 0 to 9).

Other evidence comparing different extended-fixed or PRN regimens yielded inconclusive results.

Authors' conclusions

We found that, at one year, monthly regimens are probably more effective than PRN regimens using seven or eight injections in the first year, but the difference is small and clinically insignificant. Endophthalmitis is probably more common with monthly injections and differences in costs between regimens are higher if aflibercept or ranibizumab are used compared to bevacizumab.

This evidence only applies to settings in which regimens are implemented as described in the trials, whereas undertreatment is likely to be common in real-world settings. There are no data from RCTs on long-term effects of different treatment regimens.

P L A I N   L A N G U A G E   S U M M A R Y

Comparing different injection frequencies for neovascular age-related macular degeneration

What was the aim of this review?
The aim of this Cochrane Review was to find out if anti-vascular endothelial grown factor (anti-VEGF) injections for neovascular age-related macular degeneration (nAMD) can be given less frequently than every month.

Key messages
This review found that people receiving monthly injections had slightly better vision (one or two letters more on a vision test chart, less than half-line of vision) at one year compared with people receiving injections 'as needed' (average: seven injections), but there was no

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