EFFECT OF HIGH-DOSE INTRAVITREAL AFLIBERCEPT IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: COMPARISON OF REAL-WORLD OUTCOMES WITH PHARMACOKINETIC MODEL

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BACKGROUND AND IMPORTANCE

Neovascular age-related macular degeneration (nAMD) is a leading cause of vision loss, significantly impacting patients' quality of life. Anti-vascular endothelial growth factor (VEGF) therapy, by intravitreal injection (IVI), has revolutionized nAMD management by reducing disease progression and improving visual outcomes. Recurrence of neovascular leakage and haemorrhage often follows as anti-VEGF drug levels diminish. Consequently, a substantial number of patients require IVIs every 4 to 8 weeks to sustain visual improvements achieved in the initial year of treatment. To alleviate the frequency of IVIs, research has concentrated on developing longer acting anti-VEGF agents with optimized molecular profiles and improved PK and PD properties, potentially enabling extended dosing intervals. Aflibercept (AFLI) is an anti- VEGF indicated for the treatment of nAMD. The intraocular bioavailability of AFLI follows a logarithmic distribution, and it will be effective as long as its ocular concentration saturates VEGF receptors. Below this threshold, free VEGF promotes exudation and irreversible tissue damage. Recently, a higher dose of AFLI: 8mg/0.07mL (AFLI8) was approved, compared to 2mg/0.05mL (AFLI2).

AIM AND OBJECTIVES

To evaluate the correlation between the theoretical pharmacokinetic rationale for the high-dose AFLI8 regimen and its effectiveness in patients with nAMD.

MATERIALS AND METHODS

Retrospective study of patients with nAMD with subfoveal type 1 macular neovascularization who were switched from AFLI2 to AFLI8. Inclusion criteria were long-term treatment (≥6 months) with persistence of retinal fluid detected 4 weeks after the last AFLI2 IVI. A loading phase followed by a treat-and-extend regimen with weekly intervals was used and clinical outcomes were assessed at 24 weeks or last observation. A time-dependent mathematical model was developed, using Python, to calculate AFLI concentrations with AFLI2 and AFLI8. Clinical outcomes: Best Corrected Visual Acuity (BCVA, logMAR) and Central Retinal Thickness (CRT, µm) were compared between baseline and last observation, and theoretical calculations were compared with the maximum fluid-free interval (weeks).

RESULTS

20 eyes of 20 patients were analyzed. Calculation of the theoretical intravitreal values of the 2mg dose versus the 8mg dose (Table1 and Figure1) showed a difference of 18 days (2.6 weeks), i.e. the estimated intravitreal dose after 4 weeks of the 2mg dose was expected after 6.6 weeks of the 8mg dose.

	Theoretical Concentrations (mg/ml)	
Time (weeks)	Aflibercept 2mg	Aflibercept 8mg
0	0.500000	2.000000
1	0.293365	1.173460
2	0.172126	0.688505
3	0.100992	0.403967
4	0.059255	0.237019
5	0.034767	0.139066
6	0.020399	0.081594
7	0.011968	0.047874
8	0.007022	0.028089

Table 1: Theoretical concentrations calculated for each AFLI dosage, in weeks, after IVI (mathematical model)

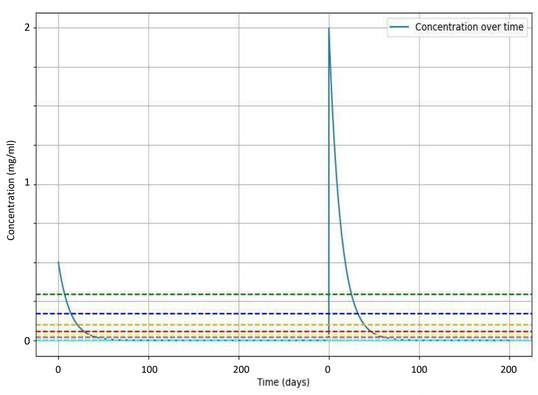

Figure 1: Anti-VEGF drug concentration calculation over time after intravitreal injections. The blue line represents drug levels, with sharp peaks at injection points and exponential decay due to clearance. Dashed lines indicate therapeutic thresholds. The X-axis (days) reflects drug duration, and the Y-axis shows VEGF expected concentrations.

Before switching from AFLI2 to AFLI8, the mean number of IVI was 8. The mean visual acuity at baseline was 0.24 ± 0.07 logMAR and the mean CRT was 345 ± 31µm. At the last observation, BCVA was 0.14 ± 0.03 logMAR (p=0.026) and CRT was 307 ± 16 µm (p=0.33).

At last observation, 4 patients (20%) still had subretinal fluid after 4 weeks (example in Figure 2), and 2 patients (10%) achieved a fluid-free interval of more than 8 weeks without recurrence (example in figure 3). A fluid-free interval of more than 4 weeks was achieved in 14 patients (70%).

The mean fluid-free interval with AFLI8 was 7 ± 0.5 weeks, and the mean difference to the fluid-free interval with AFLI2 was 3 ± 0.5 weeks.

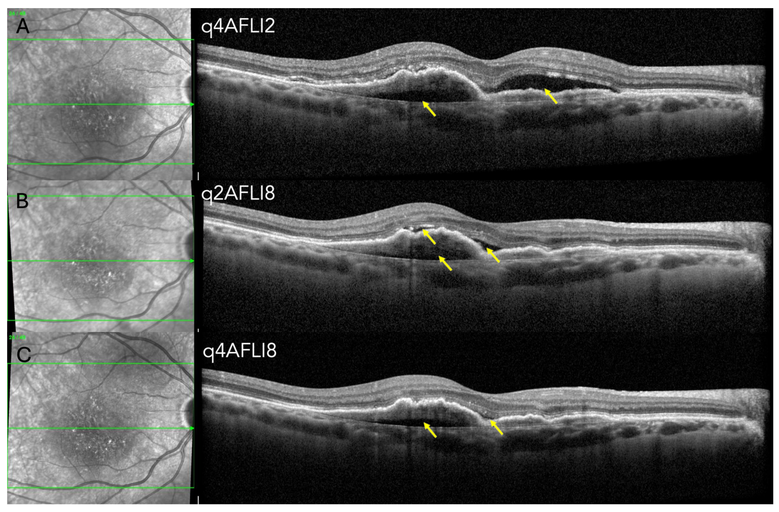

Figure 2 Optical Coherence Tomography (OCT) imaging weeks after different dosages of aflibercept in a patient with a fibrovascular pigment epithelial detachment (f-PED). (A) OCT B- scan at four weeks after intravitreal aflibercept 2 mg/0.05 mL. (B) Follow-up B-scan at two weeks after intravitreal aflibercept 8 mg/0.07 mL.(C) Follow-up B-scan at four weeks after intravitreal aflibercept 8 mg/0.07 mL. Despite the treatment modification, persistent signs of disease activity are observed in all evaluations, with the presence of subretinal fluid (yellow arrows). Until the last evaluation, the patient had been on intravitreal high dose aflibercept treatment for 14 weeks, receiving injections every four weeks, without the possibility of extending the treatment interval.

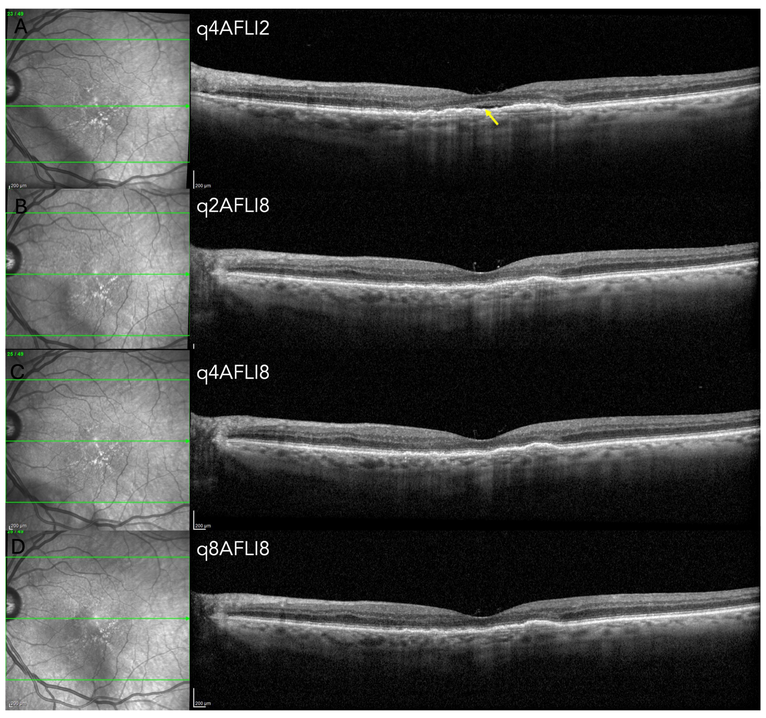

Figure 3. OCT imaging following different dosages of aflibercept in a patient with f-PED. (A) OCT B-scan of the central macula, obtained four weeks after intravitreal injection of aflibercept 2 mg/0.05 mL, demonstrating the presence of subretinal fluid over a fibrovascular pigment epithelial detachment in a patient with nAMD.(B, C, D) Sequential follow-up OCT scans at weeks 2, 4, and 8 after administration of aflibercept 8 mg/0.07 mL show resolution of neovascular exudation.

CONCLUSION AND RELEVANCE

In patients with nAMD treated with aflibercept 2mg who experienced persistent subretinal fluid at 4-week intervals, high-dose aflibercept enables improvement in functional outcomes and prolongation of fluid-free intervals by a median of 3 weeks in 70% of cases. This value seems to correspond to the theoretical increase predicted by pharmacokinetic calculations of intravitreal aflibercept dosing.

Understanding of the ocular pharmacokinetics of Aflibercept may facilitate the identification of patients who can benefit from a transition to a higher dose and predict the feasibility of extending the dosing interval.

REFERENCES

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