Analysis of treatment and comparison with simulation of treatment of nAMD with anti-VEGF agents

Luke Herbert

June 12, 2025

Abstract

This review examines treatments for neovascular age-related macular degeneration (nAMD), particularly focusing on anti-VEGF agents like aflibercept. It analyzes clinical trial evidence, real-world effectiveness, treatment discontinuation outcomes, and comparative effectiveness between different agents. Additionally, the paper explores computational modeling approaches to simulate and optimize treatment regimens, providing insights into personalized treatment strategies that may improve patient outcomes while reducing treatment burden.

1 Literature Review on Aflibercept Treatment for Neovascular AMD

Neovascular age-related macular degeneration (nAMD) represents a significant cause of vision loss in older populations. The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy has revolutionized treatment approaches, with aflibercept emerging as an effective therapeutic option.

1.1 Clinical Trial Evidence

The efficacy of aflibercept 2mg was initially established in the pivotal VIEW 1 and VIEW 2 trials, which demonstrated non-inferiority to monthly ranibizumab with bimonthly dosing after three initial monthly injections [Heier et al., 2012, Schmidt-Erfurth et al., 2014]. These studies showed a mean improvement of 8.4 letters at 52 weeks, with approximately 31% of patients gaining 15 or more letters [Heier et al., 2012].

Building on these findings, the ALTAIR study examined treat-and-extend (T&E) regimens with different adjustment intervals (2-week vs. 4-week) in Japanese patients. After 96 weeks, both groups maintained similar visual gains (+6.1 to +7.6 letters) while reducing treatment burden to approximately 10.4 injections over two years [Ohji et al., 2020]. Notably, 41.5-46.3% of patients achieved a 16-week treatment interval by week 96, suggesting significant durability potential for aflibercept in many patients.

Similar outcomes were observed in another Japanese T&E study by Maruko et al., though with a more conservative extension approach limiting intervals to 12 weeks maximum, resulting in slightly higher injection frequency (13.0 injections over two years) [Maruko et al., 2020].

1.2 Real-World Effectiveness

Despite promising clinical trial results, real-world evidence suggests more modest outcomes. In a comprehensive analysis of 49,485 eyes in the United States, Ciulla et al. found that patients received a mean of 7.3 injections in the first year but achieved only a 1-letter mean improvement [Ciulla et al., 2020]. Importantly, this study revealed a linear relationship between injection frequency and visual gains, with better outcomes observed in patients receiving 9 or more injections annually.

The gap between clinical trials and real-world outcomes highlights challenges in treatment implementation, including undertreatment and variable adherence to recommended protocols. Baseline vision also significantly impacts outcomes, with patients having worse initial vision ($\leq$20/200) gaining substantially more letters than those with better baseline vision ($\geq$20/40), who tend to experience slight vision loss despite treatment [Ciulla et al., 2020].

1.3 Treatment Discontinuation

An important clinical question concerns the possibility of discontinuing treatment after disease stabilization. Aslanis et al. investigated this in patients who had shown disease stability through three consecutive 12-week treatment intervals. Their prospective study revealed that 52.9% of patients experienced disease recurrence within 12 months after treatment cessation, with a mean time to recurrence of 6.7 months [Aslanis et al., 2022]. Notably, the presence of pigment epithelial detachment (PED) at baseline was associated with significantly higher recurrence risk (74% vs. 48%).

Despite recurrence, vision could generally be recovered with prompt retreatment, suggesting that careful monitoring after discontinuation may be a viable approach for selected patients. However, the high recurrence rate underscores nAMD's chronic nature and the need for extended monitoring even after apparent disease stability [Aslanis et al., 2022].

1.4 Comparative Effectiveness

When comparing anti-VEGF agents, the CATT study found bevacizumab to be non-inferior to ranibizumab in monthly dosing regimens [Ran, Martin et al., 2012]. Real-world comparisons among aflibercept, ranibizumab, and bevacizumab have likewise shown similar visual outcomes despite different molecular characteristics and theoretical advantages [Ciulla et al., 2020].

1.5 Conclusion

The literature on aflibercept treatment for nAMD demonstrates robust efficacy in clinical trials and reasonable effectiveness in real-world settings, though with notable differences in outcome magnitude. Treatment protocols have evolved from fixed monthly or bimonthly regimens toward individualized T&E approaches that balance treatment burden and efficacy. Future research should focus on optimizing patient selection for different treatment strategies and establishing reliable biomarkers for disease activity to guide individualized treatment decisions.

2 Parameter Extraction and Simulation Framework

2.1 Methodology for Parameter Extraction

To develop a robust simulation of aflibercept treatment for nAMD, we systematically extracted key parameters from clinical trials and real-world evidence studies. Our approach involved standardizing definitions across studies and reconciling differences between controlled trial outcomes and real-world observations.

2.2 Disease State Definitions

For simulation purposes, we standardized disease states across studies as follows:

- **NAIVE:** Patients before first injection
- **STABLE:** Patients with interval extension or maintaining maximum interval
- **ACTIVE:** Patients maintaining their current interval (except maximum interval)
- **HIGHLY_ACTIVE:** Patients requiring treatment interval reduction

2.3 Key Parameters for Simulation

Table 1 presents the consolidated parameters extracted from the literature review, categorized by parameter type and showing the source studies. These parameters form the foundation of our agent-based and discrete event simulation models.

2.4 Parameter Integration Approach

To reconcile differences between clinical trial outcomes and real-world evidence, we developed a composite approach:

- **Clinical Trial Baseline**: Visual acuity parameters and disease state transitions were primarily derived from the ALTAIR study [Ohji et al., 2020], which provided detailed treat-and-extend outcomes with aflibercept.
- **Real-World Adjustment**: We applied scaling factors based on Ciulla et al. [Ciulla et al., 2020] to adjust the clinical trial visual outcomes to real-world expectations, accounting for differences in treatment adherence, monitoring frequency, and patient selection.
- **Treatment Intensity Modifiers**: The linear relationship between injection frequency and visual outcomes identified by Ciulla et al. [Ciulla et al., 2020] was incorporated as a modifier function.
- **Baseline Vision Ceiling Effects**: Special adjustment functions were implemented to account for the observed ceiling effects in patients with good baseline vision.

2.5 Simulation Implementation

The parameters were implemented in both agent-based and discrete event simulation frameworks to model:

1. Individual patient trajectories based on treatment decisions

2. Visual acuity changes over time

3. Disease state transitions

4. Resource utilization (clinic visits, injections)

5. Treatment discontinuation and potential recurrence

The simulation incorporated three key time points from the AMD Treatment Three-Point Trajectory Model:

1. **Baseline VA** (T_0): Starting visual acuity

2. **Maximum VA** (T_{max}): Peak visual acuity after loading phase

3. **1-Year VA** (T_{12}): Visual acuity at 12 months

For T_{max}, we calculated:

$$\text{Max\_VA} = \text{Baseline\_VA} + (\text{Base\_Response} \times \text{Disease\_State\_Modifier} \times \text{Baseline\_VA\_Modifier})$$

For T_{12}, we implemented a combined approach:

$$\text{Year1\_VA} = \text{Max\_VA} + (0.6 \times \text{Intensity\_Based\_Change}) + (0.4 \times \text{Activity\_Based\_Change} \times \text{Adherence\_Factor})$$

This framework allows for comprehensive modeling of aflibercept treatment outcomes, balancing clinical trial efficacy with real-world effectiveness factors.

2.6 Premature Discontinuation Analysis

To ensure our simulation accurately captures real-world treatment patterns, we conducted a detailed analysis of premature discontinuations in the Eylea database. We defined premature discontinuations as cases where patients with good visual acuity (>20 letters) transitioned abruptly from regular treatment intervals ($\leq$2 months) to extended intervals ($\geq$6 months), suggesting a potential non-optimal treatment cessation.

2.6.1 Methodology

We analyzed the real-world dataset using the following criteria:

- Visual acuity better than 20 letters at the time of the treatment pattern change
- Treatment interval increasing from $\leq$60 days (regular treatment) to $\geq$180 days (extended interval)
- Two separate analyses: one including all identified cases, and another excluding discontinuations occurring around the one-year mark (330-390 days from treatment start), as these would be classified as "course complete but not renewed" rather than true premature discontinuations

2.6.2 Key Findings

Our analysis revealed 266 true premature discontinuations affecting 249 unique patients, with the following characteristics:

- **Visual Acuity at Discontinuation:** Mean VA of 61.7 letters (median 65.0 letters), indicating good vision at the time of discontinuation
- **Treatment Intervals:** Mean interval before discontinuation of 52.1 days (∼7.5 weeks) increasing to 411.5 days (∼59 weeks), representing an approximately 8-fold increase
- **Vision Impact:** Mean VA change of -9.4 letters following premature discontinuation, indicating significant vision loss

Notably, excluding discontinuations at the one-year mark affected only 16 cases (less than 6% of the total), suggesting that true premature discontinuations are largely distinct from planned end-of-course discontinuations.

2.6.3 Implementation in Simulation

Based on these findings, we implemented a specific "premature discontinuation" type in our simulation model with the following parameters:

The simulation model distinguishes between four discontinuation types:

- **Stable max interval:** Protocol-based discontinuations after reaching and maintaining maximum treatment interval with stable disease
- **Course complete but not renewed:** Discontinuations at the end of a standard course of treatment (typically around one year)
- **Premature:** Non-protocol based early discontinuations despite good vision and regular treatment
- **Administrative:** Random discontinuations due to insurance changes, relocation, or other non-clinical factors

This refined approach allows our simulation to more accurately reflect the diverse treatment patterns observed in real-world practice, particularly the significant impact of premature discontinuations on visual outcomes.

3 Baseline Visual Acuity Analysis

3.1 Distribution of Treatment-Naïve Visual Acuity

To establish a realistic initialization model for our simulations, we analyzed baseline (treatment-naïve) visual acuity measurements from 2,029 patients in our database. Understanding the true distribution of starting visual acuities is critical for developing accurate simulation models that reflect real-world patient populations.

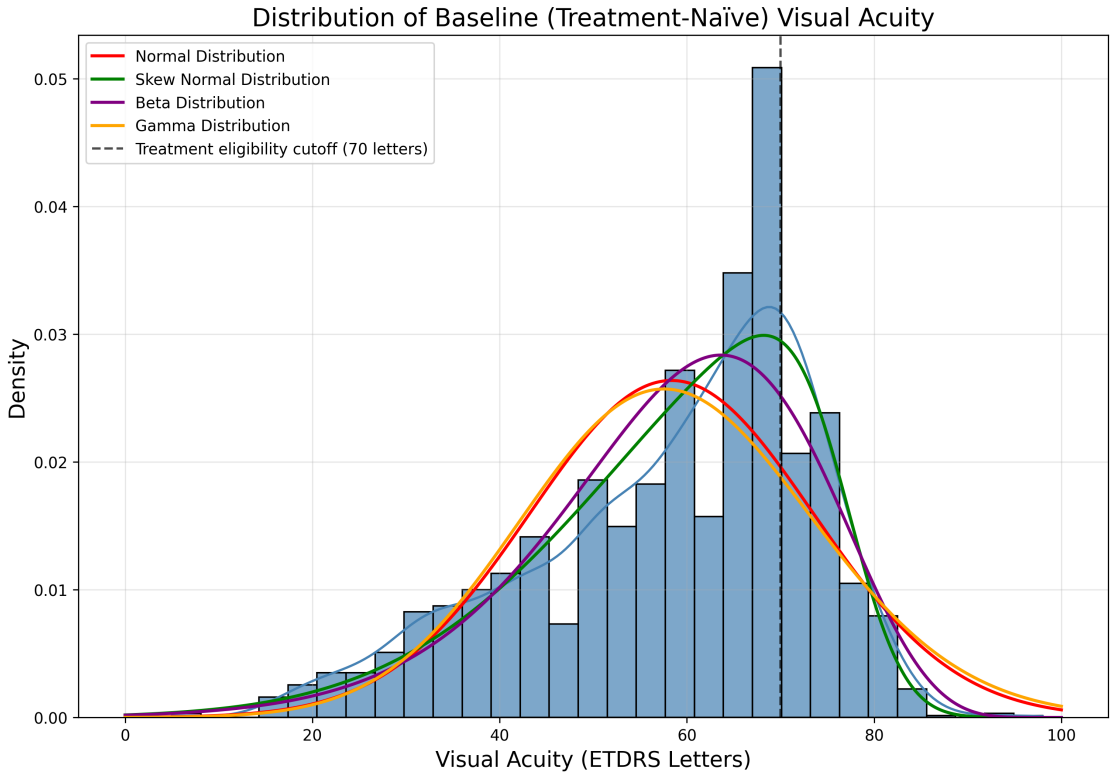

Figure 1: Distribution of baseline (treatment-naïve) visual acuity with fitted probability distributions. The dashed vertical line represents the treatment eligibility cutoff at 70 ETDRS letters.

3.2 Key Statistical Findings

Our analysis revealed several important characteristics of the baseline visual acuity distribution:

- **Central Tendency**: The mean baseline VA was 58.36 ETDRS letters (approximately 20/63 Snellen equivalent), with a median of 62.00 letters.
- **Dispersion**: The standard deviation was 15.12 letters, indicating substantial variability in baseline vision.
- **Shape Characteristics**: The distribution exhibited negative skewness (-0.72) and slight platykurtosis (-0.14), indicating more patients with lower vision than would be expected in a normal distribution.
- **Range**: Baseline VA ranged from 5.0 to 98.0 letters, with 95% of patients falling between 29.0 and 78.0 letters.

When fitted to standard probability distributions, the Beta distribution provided the best fit (lowest AIC score), capturing the non-normal characteristics of the data. This finding is important as many simulation models incorrectly assume normally distributed baseline visual acuities.

3.3 Visual Acuity Stratification

We stratified patients by baseline visual acuity ranges to better understand the clinical composition of our population:

Notably, 51.6% of patients fell within the moderate VA range (51-70 letters), aligning with the typical treatment eligibility criteria for anti-VEGF therapy in wet AMD. The small proportion of patients with excellent vision (0.2%) confirms the rarity of preserved vision in treatment-naïve wet AMD.

3.4 Treatment Eligibility Threshold Effect

The analysis confirmed the impact of the 70-letter treatment eligibility threshold, with clear distributional effects:

- Only 20.4% of patients had baseline VA above 70 letters
- The 75th percentile of the distribution was exactly at the 70-letter threshold
- The distribution shows a notable peak just below the threshold (65-69 letters)

Further investigation of patients with VA > 70 letters revealed that 57.7% showed vision decline at their second visit, with a mean decline of 4.52 letters. This suggests that many patients with good initial VA were experiencing active disease progression that warranted treatment despite being above the standard eligibility threshold.

3.5 Percentile Analysis

To provide precise reference points for our simulation model, we calculated key percentiles of the baseline VA distribution:

- 5th percentile: 29.0 letters
- 10th percentile: 35.0 letters
- 25th percentile: 50.0 letters
- 50th percentile: 62.0 letters
- 75th percentile: 70.0 letters
- 90th percentile: 75.0 letters
- 95th percentile: 78.0 letters

This percentile analysis provides evidence-based boundaries for ceiling and floor effects in vision improvement models, with the 95th percentile (78 letters) supporting our simulation model's ceiling of 85 letters as an appropriate upper bound.

3.6 Implications for Vision Change Models

Based on this analysis, we identified several key modifications needed for our simulation's vision change models:

1. **Baseline Distribution**: Initial visual acuity should be modeled using a Beta distribution rather than the previously used normal distribution, with parameters derived from our observed data.

2. **Segmented Response Profiles**: Treatment response should be segmented based on baseline VA, with differential improvement potential reflecting the ceiling effects observed in patients with better starting vision.

3. **Vision Fluctuation**: The substantial variability observed (SD = 15.12 letters) justifies implementing realistic vision fluctuations in our model.

4. **Non-responder Modeling**: The diverse outcomes observed support our implementation of non-responder proportions (15%) within the model.

These evidence-based refinements will significantly improve the clinical validity of our vision change simulations and lead to more accurate predictions of treatment outcomes across varied patient populations.

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Table 1: Key Parameters for AMD Treatment Simulation

Parameter	Value	Source	Confidence
Visual Acuity Parameters			
NAIVE treatment response	+8.4 letters (SD 1.2-1.4)	VIEW 1/2[1]; ALTAIR[2]	High
STABLE treatment response	+1.0 to +2.0 letters (SD 0.5-1.0)	ALTAIR[2]	Medium
ACTIVE treatment response	+0.5 to +1.0 letters (SD 0.5-1.0)	ALTAIR[2]	Medium
HIGHLY_ACTIVE response	-0.5 to +1.0 letters (SD 1.0-1.5)	ALTAIR[2]	Medium
Real-world mean VA change	+1.0 letter (at 1 year)	Ciulla et al.[3]	High
Disease State Transition Probabilities			
NAIVE to STABLE	0.55-0.60	ALTAIR[2]	High
NAIVE to ACTIVE	0.30-0.35	ALTAIR[2]	Medium
NAIVE to HIGHLY_ACTIVE	0.05-0.10	ALTAIR[2]	Medium
STABLE persistence	0.80-0.85	ALTAIR[2]	Medium
ACTIVE persistence	0.55-0.60	ALTAIR[2]	Medium
HIGHLY_ACTIVE persistence	0.50-0.65	ALTAIR[2]	Low
Treatment Protocol Parameters			
Loading phase injections	3	All studies	High
Initial interval	8 weeks	All studies	High
Minimum interval	8 weeks	ALTAIR[2]	High
Maximum interval	16 weeks	ALTAIR[2]	High
Extension increment	2 or 4 weeks	ALTAIR[2]	High
Mean injections (year 1)	7.3 (real-world)	Ciulla et al.[3]	High
Mean injections (2 years)	10.4 (clinical trial)	ALTAIR[2]	High
Treatment Effect by Injection Frequency			
$\leq$4 injections/year	-2 to -3 letters	Ciulla et al.[3]	High
5-6 injections/year	-0.4 to -1.6 letters	Ciulla et al.[3]	High
7-8 injections/year	+0.7 to +2.1 letters	Ciulla et al.[3]	High
9-10 injections/year	+2.4 to +3.3 letters	Ciulla et al.[3]	High
11-13 injections/year	+3.0 to +4.3 letters	Ciulla et al.[3]	High
Treatment Effect by Baseline VA			
$\leq$20/200	+13.9 letters	Ciulla et al.[3]	High
20/70-20/200	+0.8 letters	Ciulla et al.[3]	High
20/40-20/70	-0.8 letters	Ciulla et al.[3]	High
$\geq$20/40	-3.3 letters	Ciulla et al.[3]	High
Discontinuation and Recurrence Parameters			
Recurrence rate at 12 months	52.9%	Aslanis et al.[4]	High
Mean time to recurrence	6.7 $\pm$ 2.2 months	Aslanis et al.[4]	High
4-month recurrence rate	13%	Aslanis et al.[4]	High
6-month recurrence rate	33%	Aslanis et al.[4]	High
8-month recurrence rate	46%	Aslanis et al.[4]	High
VA change at recurrence	-3.6 letters	Aslanis et al.[4]	High
VA after re-treatment	-0.3 letters (from baseline)	Aslanis et al.[4]	High
PED recurrence risk	74% (vs. 48% without PED)	Aslanis et al.[4]	Medium

[1] Heier et al. (2012) VIEW 1/2 study [Heier et al., 2012]
[2] Ohji et al. (2020) ALTAIR study [Ohji et al., 2020]
[3] Ciulla et al. (2020) 49,485-eye real-world study [Ciulla et al., 2020]
[4] Aslanis et al. (2022) treatment discontinuation study [Aslanis et al., 2022]

Table 2: Premature Discontinuation Parameters

Parameter	**Value**	**Source**
Eligibility	VA $>$ 20 letters & interval $\leq$ 60 days	Real-world analysis
Annual probability	10-15%	Real-world frequency
Vision change	-9.4 letters (mean)	Real-world analysis
Monitoring frequency	More frequent than stable discontinuations	Clinical guidance
Retreatment probability	Higher than stable discontinuations	Clinical implications

Table 3: Distribution of patients by baseline visual acuity ranges

Visual Acuity Range	**Patient Count**	**Percentage**
Very Poor (0-30 letters)	118	5.8%
Poor (31-50 letters)	451	22.2%
Moderate (51-70 letters)	1,046	51.6%
Good (71-85 letters)	410	20.2%
Excellent (86-100 letters)	4	0.2%