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

Luke Herbert

May 3, 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 (20/200) gaining substantially more letters than those with better baseline vision (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.

References

Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration | New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMoa1102673.

Stamatios Aslanis, Urban Amrén, Charlotte Lindberg, and David Epstein. Recurrent Neovascular Age-Related Macular Degeneration after Discontinuation of Vascular Endothelial Growth Factor Inhibitors Managed in a Treat-and-Extend Regimen. *Ophthalmology Retina*, 6(1):15–20, January 2022. ISSN 2468-6530. doi: 10.1016/j.oret.2021.03.010.

Thomas A. Ciulla, Rehan M. Hussain, John S. Pollack, and David F. Williams. Visual Acuity Outcomes and Anti–Vascular Endothelial Growth Factor Therapy Intensity in Neovascular Age-Related Macular Degeneration Patients: A Real-World Analysis of 49 485 Eyes. *Ophthalmology Retina*, 4(1):19–30, January 2020. ISSN 2468-6530. doi: 10.1016/j.oret.2019.05.017.

Jeffrey S. Heier, David M. Brown, Victor Chong, Jean-Francois Korobelnik, Peter K. Kaiser, Quan Dong Nguyen, Bernd Kirchhof, Allen Ho, Yuichiro Ogura, George D. Yancopoulos, Neil Stahl, Robert Vitti, Alyson J. Berliner, Yuhwen Soo, Majid Anderesi, Georg Groetzbach, Bernd Sommerauer, Rupert Sandbrink, Christian Simader, and Ursula Schmidt-Erfurth. Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration. *Ophthalmology*, 119(12):2537–2548, December 2012. ISSN 0161-6420, 1549-4713. doi: 10.1016/j.ophtha.2012.09.006.

Daniel F. Martin, Maureen G. Maguire, Stuart L. Fine, Gui-shuang Ying, Glenn J. Jaffe, Juan E. Grunwald, Cynthia Toth, Maryann Redford, and Frederick L. Ferris. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration: Two-Year Results. *Ophthalmology*, 119(7):1388–1398, July 2012. ISSN 0161-6420, 1549-4713. doi: 10.1016/j.ophtha.2012.03.053.

Ichiro Maruko, Masashi Ogasawara, Akiko Yamamoto, Kanako Itagaki, Taiji Hasegawa, Hisaya Arakawa, Makiko Nakayama, Hideki Koizumi, Annabelle A. Okada, Tetsuju Sekiryu, and Tomohiro Iida. Two-Year Outcomes of Treat-and-Extend Intravitreal Aflibercept for Exudative Age-Related Macular Degeneration: A Prospective Study. *Ophthalmology Retina*, 4(8):767–776, August 2020. ISSN 2468-6530. doi: 10.1016/j.oret.2020.03.010.

Masahito Ohji, Kanji Takahashi, Annabelle A. Okada, Masato Kobayashi, Yoshimi Matsuda, Yasuhiro Terano, Masahito Ohji, Tsukasa Hanemoto, Tatsushi Kaga, Takeya Kouno, Hirokuni Kitamei, Shinpei Sato, Kanji Takahashi, Ryoji Yanai, Eiichi Uchio, Kazunori Miyata, Yoshihiro Wakabayashi, Takatoshi Maeno, Tsutomu Yasukawa, Masayuki Horiguchi, Tetsuya Nishimura, Akiteru Kawahara, Yasuo Kurimoto, Kenichi Murai, Namie Kobayashi, Wataru Kimura, Eriko Matsushita, Tomohiro Iida, Kanako Yasuda, Yuji Kato, Masahiro Miura, Annabelle Ayame Okada, Ryusaburo Mori, Atsushi Sugiyama, Yasuo Ito, Daisaku Kimura, Kei Nakai, Chota Matsumoto, Shinobu Takeuchi, Kishiko Okoshi, Yoshihisa Nuno, Yohei Nomoto, Toshio Mori, Muneyasu Takeda, Noriko Yoshida, Mio Hosokawa, Kohei Sonoda, and for the ALTAIR Investigators. Efficacy and Safety of Intravitreal Aflibercept Treat-and-Extend Regimens in Exudative Age-Related Macular Degeneration: 52- and 96-Week Findings from ALTAIR. *Advances in Therapy*, 37(3): 1173–1187, March 2020. ISSN 1865-8652. doi: 10.1007/s12325-020-01236-x.

Ursula Schmidt-Erfurth, Peter K. Kaiser, Jean-François Korobelnik, David M. Brown, Victor Chong, Quan Dong Nguyen, Allen C. Ho, Yuichiro Ogura, Christian Simader, Glenn J. Jaffe, Jason S. Slakter, George D. Yancopoulos, Neil Stahl, Robert Vitti, Alyson J. Berliner, Yuhwen Soo, Majid Anderesi, Olaf Sowade, Oliver Zeitz, Christiane Norenberg, Rupert Sandbrink, and Jeffrey S. Heier. Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration: Ninety-Six–Week Results of the VIEW Studies. *Ophthalmology*, 121(1):193–201, January 2014. ISSN 0161-6420, 1549-4713. doi: 10.1016/j.ophtha.2013.08.011.

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			
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			
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
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 ś 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]