Treatment Journey of Age-Related Macular Degeneration and Diabetic Macular Edema Patients: Analyzing Bevacizumab Persistence and Therapy Switching

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Background

- Age-related macular degeneration (AMD) and diabetic macular edema (DME) are leading causes of visual impairment. In the United States, AMD and DME affect approximately 20 million and 750,000 people, respectively.[1,2]
- Ophthalmic vascular endothelial growth factor inhibitors (OVEGFIs) are the gold standard for treating these conditions, but their high cost can be a substantial economic burden on patients and payers. Per Prime Therapeutics' book of business and Centers for Medicare & Medicaid Services (CMS) data, OVEGFIs rank as a top drug category across all 3 lines of business.[3-5]
- Bevacizumab (Avastin) is supported by the American Academy of Ophthalmology's guidelines as off-label use for AMD and DME. Its compounded nature distinguishes it from other OVEGFIs. Additionally, bevacizumab costs approximately 1/12 the price of other drugs in this category, making it the preferred first-line treatment option.[3,4,6]
- Understanding persistence to bevacizumab is crucial for optimizing formulary decisions and cost-containment strategies.[7]

Objective

The objective is to assess persistence and time to switch to alternative OVEGFIs for patients newly initiating bevacizumab therapy for AMD and DME using medical drug claims.

Methods

- **Figure 1** displays the study methods as outlined.
- Observational retrospective analysis of paid medical drug claims from July 1, 2021, to December 31, 2023.
- Study time frame:
  - 6-month lookback period: July 1, 2021, to December 31, 2021.
  - Identification period: 12-month evaluation from member's start (index) date, which must occur between January 1, 2022, and September 30, 2022.
  - Evaluation period: 15-month evaluation from member's index date.
- Study population:
  - Continuously enrolled members in commercial or Medicare coverage aged 18 and older.
  - OVEGFI-naïve, determined by no claims for bevacizumab or a non-bevacizumab ophthalmic agent in this therapeutic class during the 6-month lookback period.
  - Index bevacizumab claim was identified during the identification period using drug name and International Classification of Diseases, Tenth Revision (ICD-10) codes for AMD and DME.
    - Claim lines were flagged for treatment in the left eye, right eye, or both eyes by applying the following logic:
      - Units billed equaling the treatment of 2 eyes were assigned both eyes (i.e., 2 units for procedure code J9035 and 10 units for procedure code C9257).
      - Procedure modifier code of LT for left eye and RT for right eye.
      - ICD-10 diagnosis code descriptions (e.g., H35.531 – age-related macular degeneration, right eye).
    - Members having 1 or more claim(s) that could not be assigned to left, right, or both eyes were excluded.
  - Eyes with at least 4 dates of service were included.
- Cohorts: persistent and non-persistent
  - Determined during the identification period.
  - Calculated from the eye's index bevacizumab claim out to 365 days, with persistent eyes having 365 days of bevacizumab without clinically relevant gaps.
    - Clinically relevant gap for this study was defined as eyes not having a bevacizumab claim within the standard treatment interval (i.e., 28 days) and the following 45 days after the 28-day mark (73-day total gap from prior injection, which is approximately 2.5 months without treatment).
- Baseline characteristics of age and Elixhauser Comorbidity Index[8] were assessed between cohorts.
- Primary outcomes:
  - Days of therapy:
    - Calculated from the index date to the last day covered before a more than 45-day gap.
  - Proportion of eyes that switched OVEGFI.
  - Time to switch:
    - Defined as days to initiation of an alternative OVEGFI (index BEV claim out to 15 months).
- Secondary outcomes:
  - Switching preferencing.

Table 1

Study Population Characteristics at a Member Level

	n = 436	
	Mean/%	SD/Count
Age	70.60	10.76
% older than 65	85.78%	374
ELX score	0.23	0.59

Table 2

Primary Outcomes and Switching Behavior by Cohort at an Eye Level

Primary Outcomes

	Overall			Persistent			Non-Persistent				
Outcome	n	Mean/ Count	SD/%	n	Mean/ Count	SD/%	n	Mean/ Count	SD/%	F-Test/Wald Chi Square	P-value
Average days to significant gap (45 days) or discontinuation (index day out to 12 months)	534	215.48	110.27	146	360.68	10.41	388	160.85	75.89	992.41	< 0.001
Average days to switch (index day out to 15 months)	534	405.35	108.71	146	451.44	17.41	388	388.01	122.71	35.67	< 0.001
%/Count switched to new drug	534	129	24%	146	14	10%	388	115	30%	23.28	< 0.001
Switchers average days to switch (index day out to 15 months)	129	260.48	138.63	14	419.14	45.98	115	241.17	133.67	19.97	< 0.001

Switching Behavior

	Overall (n = 129)		Persistent (n = 14)		Non-Persistent (n = 115)		Fisher-Freeman-Halton Exact Test	
Generic Name (Brand Name)	n	%	n	%	n	%	Table Probability	Pr <= P
Ranibizumab (Lucentis)	5	3.88%	0	0.00%	5	4.35%	0.0952	0.48
Ranibizumab-eqrn (Cimerli)	4	3.10%	0	0.00%	4	3.48%		
Aflibercept (Eylea)	117	90.70%	13	92.86%	104	90.43%		
Faricimab-svoa (Vabysmo)	3	2.33%	1	7.14%	2	1.74%		

No utilization of ranibizumab-nuna (Byooviz), aflibercept (Eylea HD), or brolucizumab-dbll (Beovu)

Results

- **Study Population** (Table 1)
  - After applying the inclusion and exclusion criteria, the study sample consisted of 436 members, with 534 distinct eyes identified.
    - The average age of the analyzed sample was 76.60 (SD = 10.76), and the average Elixhauser Comorbidity Index was 0.23 (SD = 0.59).
- **Days of Therapy** (Table 2)
  - The mean days of therapy was 215.48 days (SD = 110.27), with the persistent and non-persistent cohorts averaging 360.68 (SD=10.41) and 160.85 (SD = 75.89), respectively ($F = 992.41$; $p<0.001$; Cohen's $d = 3.08$).
- **Switching Behavior** (Table 2; Figure 2)
  - Overall, 24% of eyes analyzed switched therapy, with more of the non-persistent eyes switching than persistent eyes (30% vs. 10%; $\chi2 = 23.28$; $p < 0.001$; Cohen's $d = -0.52$).
    - Of those eyes that switched therapies, the persistent eyes took longer to switch to alternative OVEGFIs than non-persistent eyes (419.14 days vs. 241.17 days).
  - The most common agent patients switched to after bevacizumab was aflibercept (Eylea), followed by ranibizumab (Lucentis), ranibizumab-eqrn (Cimerli), then faricimab-svoa (Vabysmo).

Limitations

- New start patients may have been receiving bevacizumab with different coverage.
- Inconsistent administration time frames, challenges getting office appointments, comfortability with intravitreal injections, and several other factors can influence how often a patient receives treatment.
- Complete medical claims data was not available for the identified patient sample.
- Patient population was based on commercial and Medicare lines of business, so results may not be amenable to other groups (e.g., Medicaid).
- This research was unable to determine whether patients were progressing to alternative OVEGFIs due to disease progression, non-persistence, or an alternative factor, but the assumption is that if patients are progressing due to disease progression, that should be occurring in both persistent and non-persistent populations.

Figure 1

Study Design Diagram

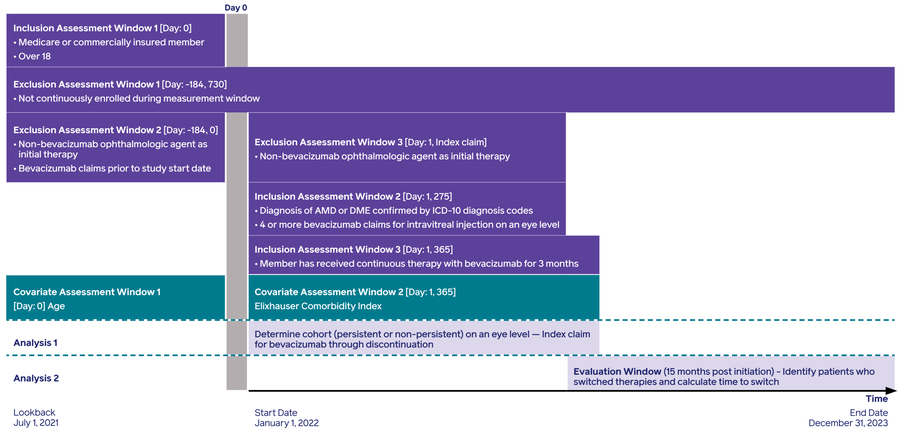
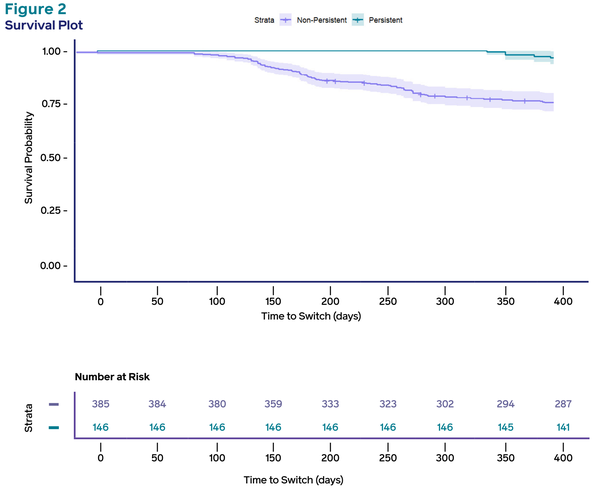


Figure 2

Survival Plot



Discussion

Upstream Management Considerations

- In a population that initiated treatment with bevacizumab, most (3 in 4) patients did not switch therapies within the first 15 months, suggesting that bevacizumab can effectively manage AMD and DME for a substantial period.
- Given the invasive nature of intravitreal injections and other challenges with receiving OVEGFIs, starting with the most cost-effective option (i.e., bevacizumab) aligns with both clinical and economic goals. This approach minimizes unnecessary exposure to higher-cost agents early in treatment.

Downstream Management Considerations

- Despite 73% of eyes not being persistent on therapy while receiving bevacizumab, most of these cases did not switch to alternative OVEGFIs. This represents an opportunity to improve persistence through interventions, such as patient and provider education, adherence support programs, or help addressing barriers like scheduling conflicts.

Implications to Stakeholders

- Payers: Encouraging persistence with bevacizumab could significantly reduce early switching and associated costs. Ensuring oversight of both first- and second-line therapies is critical as biosimilars and new agents enter the market.
- Providers: These findings support evidence-based decision-making by emphasizing bevacizumab as a viable first-line therapy, enabling providers to focus on managing treatment response and disease progression.
- Patients: Longer persistence to bevacizumab may lead to more stable clinical outcomes and reduced financial burdens by delaying transitions to more expensive treatments.

Conclusions

- Patients persistent to bevacizumab for AMD and DME had significantly longer days of therapy and were less likely to switch to alternative OVEGFIs.
- These findings suggest that interventions to maintain persistence with first-line bevacizumab could reduce switching to higher-cost therapies.

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