Ocular Adverse Events Associated with Pegcetacoplan and Avacincaptad Pegol for Geographic Atrophy: A Population-Based Pharmacovigilance Study

ZEENA KAILANI, ANDREW MIHALACHE, MARKO M. POPOVIC, PETER J. KERTES, AND RAJEEV H. MUNI

• OBJECTIVE: To evaluate the postmarketing ocular adverse events (AEs) reported for avacincaptad pegol and pegcetacoplan, the only Food and Drug Administration (FDA)–approved treatments for geographic atrophy (GA).

• DESIGN: Retrospective pharmacovigilance analysis.

• SUBJECTS: Ocular AE reports in the FDA Adverse Event Reporting System (FAERS) in which pegcetacoplan or avacincaptad pegol was identified as the primary suspect drug were analyzed.

• METHODS: Using the OpenVigil 2.1 data mining software, we conducted a retrospective pharmacovigilance analysis of the FAERS database from inception to December 2024. We conducted disproportionality analyses to assess reporting odds ratios (RORs) for specific drug-AE combinations compared with all other drugs in the database.

• MAIN OUTCOME MEASURES: Ocular AEs were evaluated.

• RESULTS: A total of 752 and 80 patients with AEs secondary to pegcetacoplan and avacincaptad pegol, respectively, were identified. Ocular AEs disproportionately overreported for pegcetacoplan included anterior segment (iris) hemorrhage (ROR 1767, 95% CI 538-5803), iris neovascularization (ROR 1248, 95% CI 502-3099), choroidal neovascularization (ROR 1328, 95% CI 956-1845), intraocular injection complication (ROR 2552, 95% CI 1607-4053), hemorrhagic occlusive retinal vasculitis (ROR 4606, 95% CI 2000-10,611), retinal occlusive vasculitis (ROR 2352, 95% CI 1313-4212), and bacterial endophthalmitis (ROR 1260, 95% CI 613-2589). Ocular AEs disproportionately overreported for avacincaptad pegol included choroidal neovascularization (ROR 1169, 95% CI 426-3205), vitritis (ROR 782, 95% CI 316-1936), dry age-related macular degeneration (ROR 684, 95% CI 316-1936), and cystoid macular edema (ROR 445, 95% CI 140-1412).

• CONCLUSIONS: Current prescribing patterns indicate that a broader spectrum of ocular AEs were reported for pegcetacoplan than avacincaptad pegol. These findings aim to enhance clinicians' understanding of the safety profiles of these agents, enabling informed patient care and heightened vigilance of these novel GA treatments.

Geographic atrophy (GA) is an advanced form of dry age-related macular degeneration (AMD) which represents a leading cause of irreversible central vision loss in adults aged ≥50 years.[1,2] Characterized by progressive degeneration of the retinal pigment epithelium (RPE), photoreceptors, and choriocapillaris, GA results in the formation and subsequent expansion of atrophic regions in the macula.[1-4] Unlike neovascular AMD, there are a lack of therapeutic modalities for GA. Indeed, before the approval of the intravitreal agents pegcetacoplan and avacincaptad pegol in 2023, there were no GA therapies approved by the US Food and Drug Administration (FDA).[1,2,4-6]

Pegcetacoplan and avacincaptad pegol target key components of the complement pathway.[4] Pegcetacoplan's inhibition of C3 and avacincaptad pegol's targeting of C5 both serve to reduce complement-mediated inflammation and, in turn, prevent the expansion of atrophic lesions.[4,7-9] Despite promising results in early clinical trials, severe ocular adverse events (AEs) have been reported for both agents, including new-onset neovascular AMD, intraocular inflammation, ischemic optic neuropathy, and increased intraocular pressure.[4,7,9-11]

To our knowledge, a comprehensive investigation into the safety profiles of pegcetacoplan and avacincaptad pegol

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in real-world settings has not yet been conducted. The FDA Adverse Event Reporting System (FAERS) database is a postmarketing drug safety surveillance program that compiles AE information voluntarily submitted to the FDA.[12] This investigation systematically evaluated all reports of ocular AEs attributed to pegcetacoplan and avacincaptad pegol using FAERS data.

METHODS

We conducted a retrospective pharmacovigilance study. Real-world pharmacovigilance data were sourced from the FAERS database, which collects postmarketing reports of AEs voluntarily submitted by consumers, health care professionals, and pharmaceutical companies.[12] This study focused specifically on reports of AEs in which avacincaptad pegol and pegcetacoplan were identified as the primary suspect drugs.

Using OpenVigil 2.1 software (Kiel, Germany),[13] we analyzed FAERS data from the fourth quarter of 2003 to the fourth quarter of 2024. AEs related to each drug were captured following their approval. However, the entire FAERS database time frame was included to establish a stable and robust background reporting rate for comparison.

We evaluated reports of AEs attributed to these drugs compared to the background rates observed across all drugs in the FAERS database.[12] To assess disproportionality, we used reporting odds ratios (RORs), which indicated the odds of a specific AE being reported for the drug of interest compared with all other drugs in the FAERS database.

To detect positive safety signals for avacincaptad pegol and pegcetacoplan, we applied the following criteria described by Evans and associates[14]: drug-event combinations with at least 3 reports, a χ^2 value greater than 4, and a proportional reporting ratio greater than 2. To further minimize the risk of false-positive findings, we employed Bayesian confidence propagation neural network (BCPNN) algorithms.[15] Drug-event combinations were considered disproportionately overreported if the lower bound of the 95% CI for the information component (IC) was positive (i.e., $IC_{025} > 0$).[15]

RESULTS

• **PEGCETACOPLAN:** A total of 752 unique patients with AEs secondary to pegcetacoplan were identified over the study period. Of these, 84 patients (11%) were female, 50 (7%) were male, and the sex of the remaining patients was not specified. The mean age across reports was 75.7 ± 15.7, and most reports originated from the United States (n=578, 77%).

The following ocular AEs were significantly overreported for pegcetacoplan: corneal edema (n=10, ROR 126, 95% CI 67.2-235), anterior chamber cell (n=10, ROR 385, 95% CI 205-724), anterior chamber inflammation (n=3, ROR 141, 95% CI 45.3-441), hyphema (n=5, ROR 270, 95% CI 111-655), anterior chamber (iris) hemorrhage (n=3, ROR 1767, 95% CI 538-5803), iritis (n=14, ROR 148, 95% CI 86.8-251), iris neovascularization (n=5, ROR 1248, 95% CI 502-3099), choroidal neovascularization (n=40, ROR 1328, 95% CI 956-1845), intraocular injection complication (n=21, ROR 2552, 95% CI 1607-4053), vitritis (n=19, ROR 308, 95% CI 194-487), vitreous opacities (n=5, ROR 161, 95% CI 66.3-388), vitreous floaters (n=44, ROR 152, 95% CI 112-207), hemorrhagic occlusive retinal vasculitis (n=7, ROR 4607, 95% CI 2000-10611), retinal occlusive vasculitis (n=13, ROR 2352, 95% CI 1313-4212), retinal vasculitis (n=12, ROR 260, 95% CI 147-462), retinal ischemia (n=4, ROR 188, 95% CI 69.9-504), neovascular AMD (n=15, ROR 378, 95% CI 226-634), subretinal fluid (n=4, ROR 105, 95% CI 39.0-280), bacterial endophthalmitis (n=8, ROR 1260, 95% CI 613-2589), and staphylococcal eye infection (n=3, ROR 344, 95% CI 110-1082).

A graphical depiction of the results of our disproportionality analysis of pegcetacoplan can be found in Figure 1. A comprehensive summary of ocular AEs that were overreported for pegcetacoplan, including those with ROR values less than 100, can be found in Table 1.

• **AVACINCAPTAD PEGOL:** A total of 80 unique patients with AEs secondary to avacincaptad pegol were identified over the study period. Of these, 46 (58%) patients were female, 19 (24%) were male, and the sex of the remaining patients was not specified. The mean age across reports was 83.7 ± 10.0 years. All reports originated from the United States.

The following ocular AEs were disproportionately overreported for avacincaptad pegol: choroidal neovascularization (n=4, ROR 1169, 95% CI 426-3205), vitritis (n=5, ROR 782, 95% CI 316-1936), vitreous floaters (n=6, ROR 197, 95% CI 85.7-453), optic ischemic neuropathy (n=3, ROR 304, 95% CI 95.7-963), dry AMD (n=3, ROR 684, 95% CI 215-2172), cystoid macular edema (n=3, ROR 445, 95% CI 140-1412), endophthalmitis (n=5, ROR 228, 95% CI 92.1-564), and eye inflammation (n=4, ROR 130, 95% CI 47.7-356).

A graphical depiction of the results of our disproportionality analysis of avacincaptad pegol can be found in Figure 2. A comprehensive summary of ocular AEs that were overreported for avacincaptad pegol, including those with ROR values less than 100, can be found in Table 1.

Our disproportionality analysis identified 9 ocular AEs that were overreported for both pegcetacoplan and avacincaptad pegol, including choroidal neovascularization (pegcetacoplan: n=40, ROR 1328, 95% CI 956-1845; avacincaptad pegol: n=4, ROR 1169, 95% CI 426-3205), vitritis

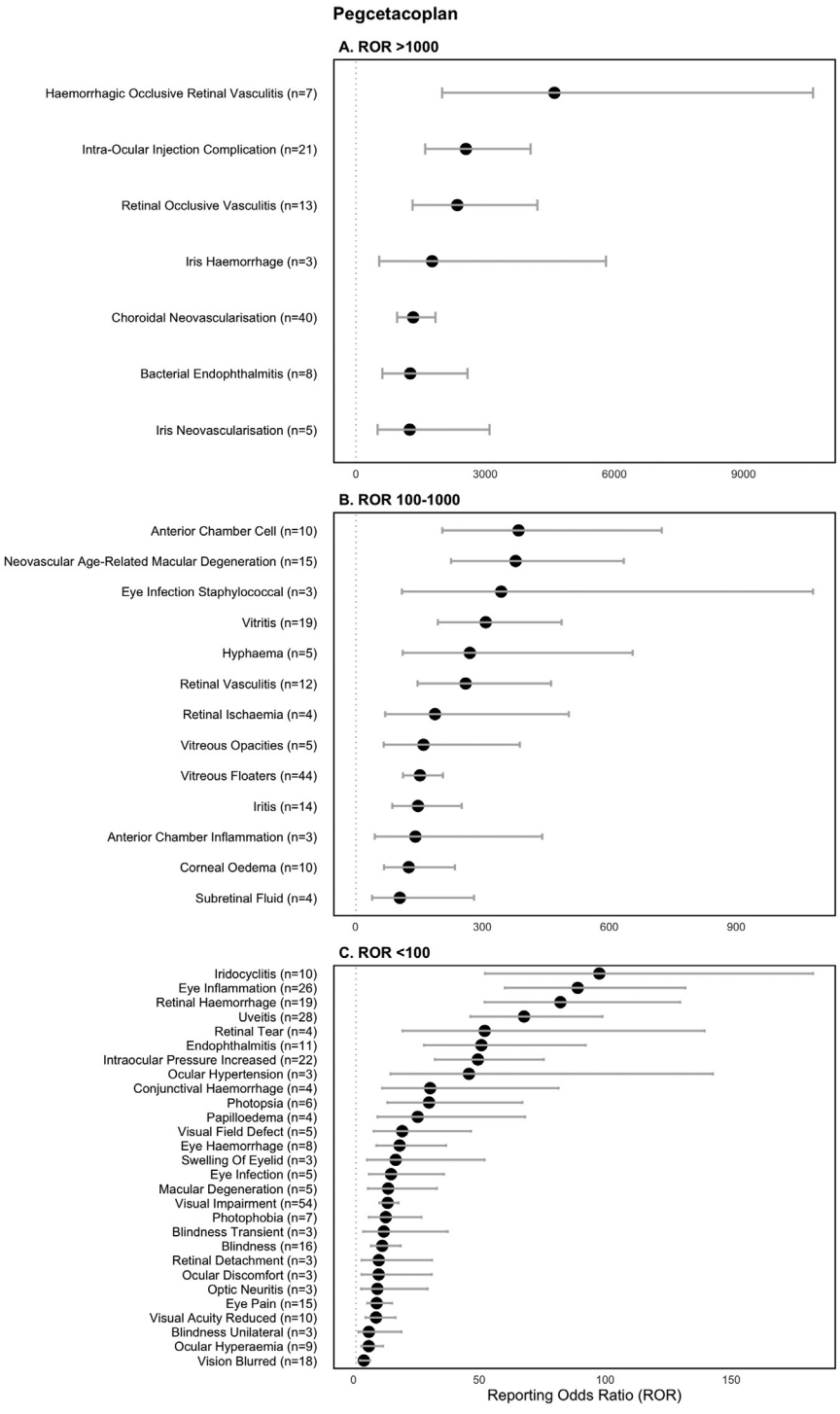

FIGURE 1. Disproportionality analysis for adverse events of pegcetacoplan. Reporting odds ratios (RORs) are presented with their 95% CIs.

(pegcetacoplan: n=19, ROR 308, 95% CI 194-487; avacincaptad pegol: n=5, ROR 782, 95% CI 316-1936), vitreous floaters (pegcetacoplan: n=44, ROR 152, 95% CI 112-207; avacincaptad pegol: n=6, ROR 197, 95% CI 85.7-453), endophthalmitis (pegcetacoplan: n=11, ROR 50.8, 95% CI 28.0-92.2; avacincaptad pegol: n=5, ROR 228, 95% CI 92.1-564), eye inflammation (pegcetacoplan: n=26, ROR 89.0, 95% CI 60.2-132; avacincaptad pegol: n=4, ROR 130, 95% CI 47.7-356), eye pain (pegcetacoplan: n=15, ROR 9.18, 95% CI 5.51-15.3; avacincaptad pegol: n=5, ROR 30.1, 95% CI 12.2-74.4), blurred vision (pegcetacoplan: n=18, ROR 4.13, 95% CI 2.58-6.58; avacincap-

TABLE 1. Overview of Statistically Significant RORs Following Primary Suspect Analysis for Pegcetacoplan and Avacincaptad Pegol

Ocular AE	n	ROR (95% CI)
Pegcetacoplan	552	
Visual impairment	54	13.6 (10.3-17.9)
Vitreous floaters	44	152.1 (112-206)
Choroidal neovascularization	40	1328 (956-1845)
Uveitis	28	67.7 (46.4-98.9)
Eye inflammation	26	89.0 (60.2-131.8)
Intraocular pressure increased	22	49.4 (32.3-75.6)
Intraocular injection complication	21	2552 (1607-4053)
Retinal hemorrhage	19	82.177 (52.1-130)
Vitritis	19	308 (194-487)
Blurred vision	18	4.13 (2.58-6.58)
Blindness	16	11.4 (6.94-18.7)
Eye pain	15	9.18 (5.51-15.3)
Neovascular age-related macular degeneration	15	378 (226-634)
Iritis	14	148 (86.8-251)
Retinal occlusive vasculitis	13	2352 (1313-4212)
Retinal vasculitis	12	260 (146-462)
Endophthalmitis	11	50.8 (28.0-92.2)
Reduced visual acuity	10	8.94 (4.79-16.7)
Iridocyclitis	10	97.6 (52.2-183)
Corneal edema	10	126 (67.2-235)
Anterior chamber cell	10	385 (205.-724)
Ocular hyperemia	9	6.06 (3.14-11.7)
Eye hemorrhage	8	18.3 (9.12-36.8)
Bacterial endophthalmitis	8	1260 (613-2589)
Photophobia	7	12.8 (6.09-27.0)
Hemorrhagic occlusive retinal vasculitis	7	4606 (2000-10611)
Photopsia	6	30.0 (13.4-67.1)
Macular degeneration	5	13.7 (5.70-33.1)
Eye infection	5	14.9 (6.18-35.9)
Visual field defect	5	19.3 (8.03-46.6)
Vitreous opacities	5	161 (66.3-388)
Hyphema	5	270 (111-655)
Iris neovascularization	5	1248 (502-3099)
Papilledema	4	25.5 (9.54-68.2)
Conjunctival hemorrhage	4	30.5 (11.4-81.4)
Retinal tear	4	52.1 (19.5-139)
Subretinal fluid	4	105 (39.0-280)
Retinal ischemia	4	188 (69.9-504)
Blindness unilateral	3	6.11 (1.97-19.0)
Optic neuritis	3	9.47 (3.05-29.4)
Ocular discomfort	3	10.0 (3.22-31.1)
Retinal detachment	3	10.0 (3.22-31.1)
Blindness transient	3	12.0 (3.87-37.4)
Swelling of eyelid	3	16.7 (5.39-52.1)
Ocular hypertension	3	45.9 (14.7-143)
Anterior chamber inflammation	3	141 (45.3-441)
Eye infection staphylococcal	3	344 (110-1082)
Iris hemorrhage	3	1767 (538-5803)
Avacincaptad pegol	53	
Visual impairment	8	19.5 (9.37-40.4)
Vitreous floaters	6	197 (85.7-453)
Endophthalmitis	5	228 (92.1-564)
Eye pain	5	30.1 (12.2-74.3)

(*continued on next page*)

TABLE 1. (*continued*)

Ocular AE	n	ROR (95% CI)
Vitritis	5	782 (316-1936)
Choroidal neovascularization	4	1169 (426-3205)
Eye inflammation	4	130 (47.7-356)
Blurred vision	4	8.85 (3.24-24.2)
Cystoid macular edema	3	445 (140-1412)
Dry age-related macular degeneration	3	684 (215-2172)
Optic ischemic neuropathy	3	304 (95.7-963)
Reduced visual acuity	3	25.8 (8.15-81.9)

AEs = adverse events, n = number of reports, ROR = reporting odds ratio.

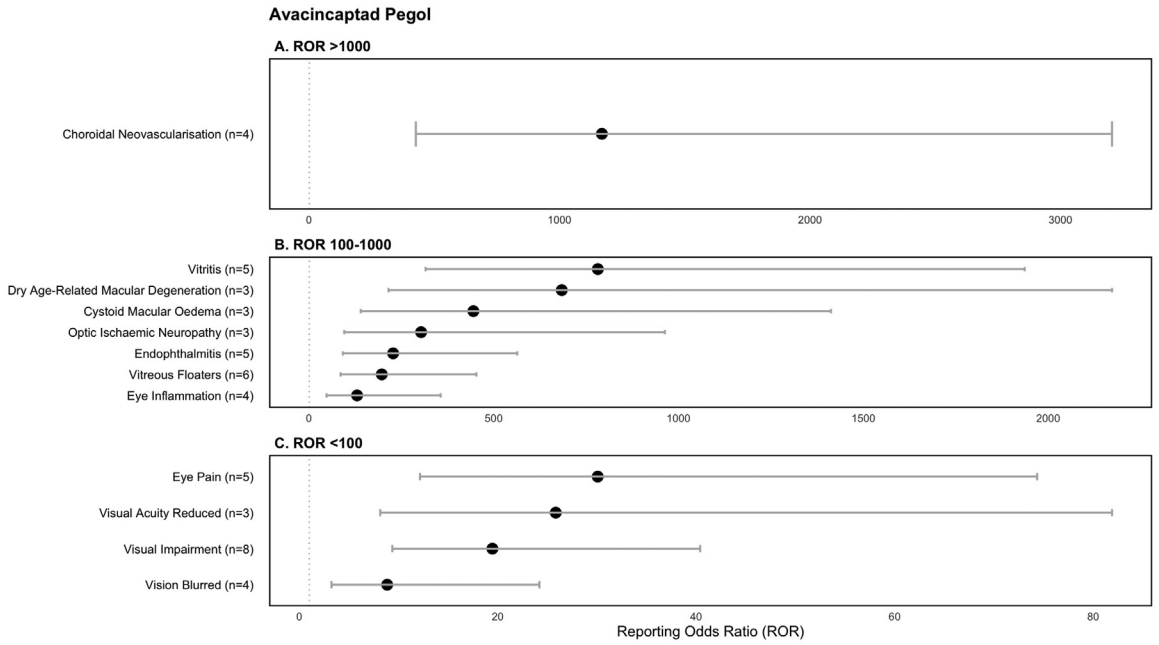

FIGURE 2. Disproportionality analysis for adverse events of avacincaptad pegol. Reporting odds ratios (RORs) are presented with their 95% CIs.

tad pegol: n=4, ROR 8.85, 95% CI 3.24-24.2), reduced visual acuity (pegcetacoplan: n=10, ROR 8.94, 95% CI 4.79-16.7; avacincaptad pegol: n=3, ROR 25.8, 95% CI 8.15-81.9), and visual impairment (pegcetacoplan: n=54, ROR 8.94, 95% CI 4.79-16.7; avacincaptad pegol: n=8, ROR 19.5, 95% CI 9.37-40.4).

A graphical depiction of ocular AEs that were overreported for both drugs can be found in Figure 3.

DISCUSSION

The approval of pegcetacoplan and avacincaptad pegol by the FDA marked a significant advancement for the treatment of GA. Although these agents have redefined the management of GA, their associated ocular AEs must be carefully evaluated. To our knowledge, our investigation represents the first comprehensive, postmarketing pharmacovigilance analysis for pegcetacoplan and avacincaptad pegol in this context. Our findings shed light on the spectrum of potential ocular AEs attributed to these therapies, providing valuable evidence to guide clinical decision making and patient counseling as their use expands in ophthalmic practice.

Although real-world evidence on ocular AEs attributed to pegcetacoplan and avacincaptad pegol remains limited in the literature, clinical trials have documented several important AEs. In the phase 3 OAKS and DERBY trials (n=1258), 61.6% of patients receiving monthly pegcetacoplan had treatment-emergent AEs in the study eye by month 24, compared with 55% in the bimonthly group and

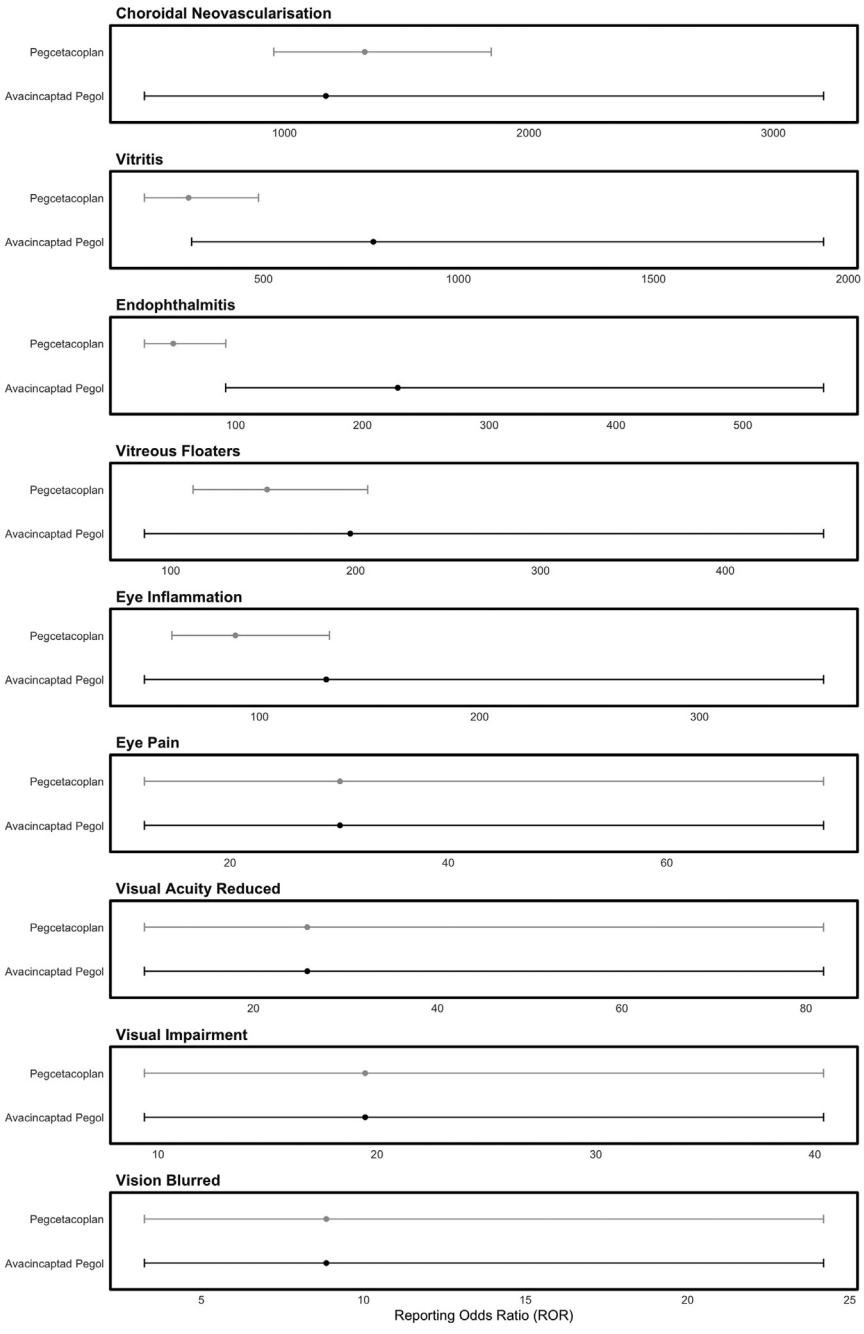

FIGURE 3. Ocular adverse events found to be overreported for both pegcetacoplan and avacincaptad pegol. Reporting odds ratios (RORs) are presented with their 95% CIs.

46.3% in the sham group.[9] Reported AEs included vitreous floaters, new-onset exudative AMD, retinal hemorrhage, and decreased visual acuity, with 3 serious cases of ischemic optic neuropathy documented.[9]

Similarly, in the GATHER1 phase 2/3 trial of avacincaptad pegol (n=286), ocular treatment-emergent AEs were observed in 58.2% of patients receiving 2 mg of avacincaptad pegol, which is the FDA-approved dosage, and 73.5% receiving 4 mg, compared with 40.9% in the sham group.[16] Ocular AEs occurring at a frequency of ≥2% in the study cohorts (n=150) at month 18 included conjunctival hyperemia (8%), conjunctival edema (4.7%), punctate keratitis (6.7%), cataracts (4%), vitreous detachment (4%), choroidal neovascularization (14%), eye pain (6.7%), and visual acuity reduction (4%).[16] Moreover, the GATHER2 phase 3 trial (n=447) reported ocular treatment-emergent AEs in 49% of patients treated with 2 mg avacincaptad pegol compared with 37% in the sham group.[11] Ocular AEs occurring in ≥2% of the study cohort (n=225) at month 12 included conjunctival hyperemia (5.3%), dry

eye (3.6%), punctate keratitis (4.9%), increased intraocular pressure (12%), vitreous detachment (3.1%), macular neovascularization (6.7%), and eye pain (4%).[11] Although clinical trial data suggest a comparable rate of ocular AEs between pegcetacoplan and avacincaptad pegol, our pharmacovigilance analysis identified a broader range of ocular AEs currently reported for pegcetacoplan. We do caution that our findings are also subject to the real-world use of these agents, but that they emphasize the necessity of a proactive, risk-based approach to patient management. They also underscore the importance of continuous monitoring and thorough patient counseling to address the potential ocular AEs linked to these therapies.

The disproportionality analysis revealed significantly elevated RORs for ocular AEs associated with pegcetacoplan, including but not limited to anterior segment (iris) hemorrhage (ROR 1767), iris neovascularization (ROR 1248), choroidal neovascularization (ROR 1328), hemorrhagic occlusive retinal vasculitis (ROR 4606), retinal occlusive vasculitis (ROR 2352), and bacterial endophthalmitis (ROR 1260). These severe safety signals highlight the need for close monitoring when administering intravitreal pegcetacoplan. We do note that there were no retinal vasculitis events in FAERS AE reports of avacincaptad pegol. Most ocular AEs identified in this analysis for pegcetacoplan align closely with those documented in clinical trials and listed in the FDA package labels, such as retinal detachment, retinal vasculitis, neovascular AMD, intraocular inflammation, and vitreous floaters.[17-19]

Our pharmacovigilance analysis revealed a relatively narrower risk profile as of this writing for avacincaptad pegol, with relatively fewer absolute counts of reported ocular AEs. The 5 ocular AEs showing the most disproportionately high reporting with avacincaptad pegol were choroidal neovascularization (ROR 1,169), vitritis (ROR 782), dry AMD (ROR 684), cystoid macular edema (ROR 445), and optic ischemic neuropathy (ROR 304). Despite the lower absolute counts of reported ocular AEs, avacincaptad pegol exhibited relatively higher point estimates of ROR values for most ocular AEs that were overreported for both agents, as shown in Figure 3. However, its notably wider CIs compared with pegcetacoplan reflect a greater level of uncertainty, likely because of the smaller sample size available for the analysis of avacincaptad pegol.

In addition, the ocular AEs for avacincaptad pegol differed somewhat from those reported in clinical trials and the drug's FDA label.[20] Specifically, AEs that are noted in the drug's FDA label, such as increased intraocular pressure, retinal detachment, and neovascular AMD, did not emerge as significant safety signals in the FAERS database.[12] Despite this, clinicians must maintain a high level of vigilance, as the potential for ocular AEs underscores the need for careful monitoring during treatment initiation and follow-up.

The higher absolute number of ocular AEs reported for pegcetacoplan in the FAERS database suggests that it may either pose a greater intrinsic risk, provoke more noticeable adverse reactions, or simply be prescribed more frequently in patients than avacincaptad pegol. Indeed, it is important to consider that avacincaptad pegol received FDA approval 6 months later than pegcetacoplan (August 2023 vs February 2023, respectively),[4] which could partially account for the discrepancy in the number of reported AEs.

Pegcetacoplan's earlier approval and longer market presence likely allowed for greater real-world exposure, increasing the likelihood of AE identification and reporting, and ultimately providing a more extensive data set for safety evaluations. For instance, more than 210,000 vials of Izervay (avacincaptad pegol) have been distributed from FDA approval through December 2024, compared with more than 510,000 vials of Syfovre (pegcetacoplan).[21,22] Thus, the larger volume of AE reports for pegcetacoplan may reflect higher commulative distribution of the drug rather than inherent safety differences. In addition, clinicians' extended experience with pegcetacoplan may have also improved their ability to recognize and report its AEs. Conversely, avacincaptad pegol's shorter availability may lead to underreporting because of limited exposure or uncertainty in AE recognition. As such, pegcetacoplan was noted to have a considerably higher cumulative count of AEs in the FAERS database by the end of the third quarter of 2024 compared with avacincaptad pegol.

These temporal differences underscore the need for ongoing surveillance of AEs for both agents to better elucidate the long-term implications of their mechanisms of action and inform their safe use in clinical practice. Moreover, head-to-head real-world use trials are needed to directly compare the safety profiles of pegcetacoplan and avacincaptad pegol. Until avacincaptad pegol amasses comparable postmarketing data, caution is warranted when drawing conclusions about their relative safety profiles.

The inherent limitations of FAERS data, including potential reporting biases, duplicate and incomplete reports, lack of verification of report information, variability in AE definitions, possible underreporting, the inability to establish causal relationships or incidence rates, and the scarcity of data on dosing regimens and treatment duration before the onset of AEs must be acknowledged when interpreting these findings.[12] Given the spontaneous voluntary reporting to the FAERS database, the associations in our study cannot be interpreted as causative relationships. Moreover, there was a scarcity of data on the dosing regimens used, leading to the AEs reported. It is critical to consider that pegcetacoplan is also used to treat paroxysmal nocturnal hemoglobinuria and C3 glomerulopathy via systemic administration, and the inability of FAERS to differentiate between systemic and intravitreal uses of the drug likely increased the overall denominator of AE reports used in the calculation of RORs, thereby diminishing the observed safety signals of the drug.[23,24] In contrast, avacincaptad pegol is solely indicated for GA, which likely contributed to

the higher RORs associated with its AEs. To substantiate the safety signals identified in our pharmacovigilance study, further research is essential, particularly through long-term observational and cohort studies.

CONCLUSION

This pharmacovigilance study represents the first comprehensive postmarketing comparison of FAERS data for pegcetacoplan and avacincaptad pegol, currently revealing a broader ocular AE profile for pegcetacoplan, consistent with clinical trial data and FDA labeling, compared with the relatively fewer and less consistent AEs observed for avacincaptad pegol. These findings enhance premarket insights while emphasizing the need for further validation in larger, more diverse populations to establish causality and refine the comparative safety profiles of these treatments for GA. Future research should prioritize identifying high-risk patient subgroups and exploring predictive biomarkers for adverse therapeutic responses. Such efforts could improve risk stratification and support the development of personalized treatment strategies, ultimately optimizing outcomes for patients with GA.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Zeena Kailani: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Andrew Mihalache:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Marko M. Popovic:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Peter J. Kertes:** Writing – review & editing, Supervision. **Rajeev H. Muni:** Writing – review & editing, Supervision.

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Data Sharing Statement: The data analyzed in this study are publicly available through the FDA Adverse Event Reporting System (FAERS) and can be accessed via OpenVigil 2.1 (https://openvigil.sourceforge.net/).

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