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RESEARCH ARTICLE

Incidence of Recurrent Choroidal Neovascularization Following Treatment with Pegcetacoplan for Geographic Atrophy in Exudative Age-Related Macular Degeneration Patients with Inactive Choroidal Neovascularization

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Abstract

Purpose: To evaluate exudative age-related macular degeneration (AMD) patients with inactive choroidal neovascularization (CNV), pegcetacoplan treated geographic atrophy (GA) and on pro re nata (PRN) anti-Vascular Endothelial Growth Factor (VEGF) rates of CNV recurrence.

Methods: This retrospective cohort study from 2019 to 2024 included 43 exudative AMD patients with co-existing GA who received pegcetacoplan treatment and 58 control patients with exudative AMD and co-existing GA who were not treated with pegcetacoplan, all maintained on PRN anti-VEGF regimens with inactive CNV not requiring treatment for ≥6 months. The primary outcome measures was the incidence rate of recurrent CNV, defined as reactivation of CNV lesions requiring anti-VEGF treatment. Statistical analyses compared outcomes between groups.

Results: Over 13 months, the 23 pegcetacoplan patients (53%, 95% CI 39-68%) experienced recurrent CNV with an incidence rate of 1.23 (95% CI 0.73-1.73) recurrences/person-year. The 29 control patients (50%, 95% CI 37-63%) experienced recurrent CNV over 5 years, with an incidence rate of 0.21 (95% CI 0.11-0.31) recurrences/person-year. The incidence rate ratio for recurrence was 5.891 (p=0.003) for the pegcetacoplan group compared to the control.

Conclusions: This study found a significantly increased incidence of recurrent CNV in exudative AMD with inactive CNV patients on PRN anti-VEGF after pegcetacoplan treatment for GA. Findings suggest a potential relative contraindication to pegcetacoplan use and CNV reactivation. A similar proportion of patients in the control group experienced reactivation, but the pegcetacoplan group experienced recurrences over a much shorter time. Close monitoring for recurrent CNV is advised when using pegcetacoplan in this population.

Keywords: Choroidal Neovascularization, Pegcetacoplan, Geographic Atrophy, Exudative Age-Related Macular Degeneration, Recurrence, Inactive, Anti-VEGF.

1. Introduction

Age-related macular degeneration (AMD) is a progressive degenerative disease and a leading cause of vision loss in the elderly[1–3]. Two specific forms of late disease may exist either separately or concurrently: geographic atrophy (GA) and choroidal neovascularization (CNV)[4–7]. The exudative (wet) form is characterized by the abnormal growth of

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blood vessels from the choroid into the subretinal space[4]. These fragile vessels can leak fluid and blood, causing retinal damage and vision impairment if left untreated[8].

The introduction of anti-Vascular Endothelial Growth Factor (anti-VEGF) therapies, such as ranibizumab, aflibercept, brolucizumab, and faricimab, has revolutionized the treatment of exudative AMD. These agents inhibit VEGF, a key mediator of pathological angiogenesis and vascular permeability, thereby reducing CNV activity and exudation[9–16].

While anti-VEGF therapy can effectively control CNV and preserve vision in many patients, some progress to GA, the advanced nonexudative form of AMD characterized by irreversible retinal pigment epithelium (RPE) and photoreceptor cell death[6,11,17–21]. GA is a leading cause of severe vision loss in AMD, and no approved treatments were available until recently[6,8,22,23]. It is thought that GA and retinal cell death develop as a result of inflammation mediated via multiple pathways, including the complement cascade and the NLRP3 inflammasome, which are triggered by products of oxidative stress, such as drusen and lipofuscin/A2E[19,20,24].

Pegcetacoplan is a novel complement inhibitor that targets complement protein C3, a key driver of the alternative complement pathway implicated in the pathogenesis of GA[22,25]. By inhibiting C3, pegcetacoplan has shown promise in slowing the progression of GA as well as reducing photoreceptor degeneration in areas outside of GA in phase 3 clinical trials[8,22,26]. Pegcetacoplan was FDA approved for treatment of nonexudative macular degeneration with geographic atrophy in February 2023[27].

Pegcetacoplan was shown to have an increased incidence of new CNV in previously dry AMD patients compared to control in clinical trials[8,22,27]. However, the potential impact of pegcetacoplan on the risk of recurrent CNV in patients with exudative AMD with inactive CNV is not well understood. Many retina specialists adopt a pro re nata (PRN, as-needed) dosing regimen for anti-VEGF agents in patients with inactive CNV, where patients receive injections only when signs of active CNV, such as subretinal or intraretinal fluid are present[10,28,29]. This approach aims to reduce treatment burden while maintaining visual acuity but raises concerns about the potential risk of CNV reactivation during extended treatment breaks. Some providers are utilizing pegcetacoplan in patients with both GA and active CNV as well as patients with GA and inactive CNV, but these populations are not well studied as patients with prior exudative AMD were excluded from clinical trials. We hypothesize that patients with inactive CNV treated with pegcetacoplan are more likely to have recurrent active CNV.

This study aimed to evaluate the incidence of recurrent CNV in exudative AMD patients with inactive CNV treated with pegcetacoplan for GA and subsequently maintained on a PRN anti-VEGF schedule.

2. Materials and Methods

This is a retrospective cohort study performed at a large retina practice in northeast Ohio (Retina Associates of Cleveland, Inc.) between August 2019 and March 2024. The practice management system was used to identify patients with diagnosis of exudative macular degeneration with co-existing macular atrophy. Patient charts were then examined in the electronic medical record system to create a pegcetacoplan treatment group and control group. At all visits, patients underwent comprehensive ophthalmic examinations, including best corrected visual acuity (BCVA), slit-lamp biomicroscopy, dilated fundus examination, and optical coherence tomography (OCT) at baseline and follow-up visits. Treatment decisions were based on imaging findings and clinical assessments by experienced retina specialists. Patients were eligible for inclusion if they were treated on a PRN anti-VEGF regimen for inactive exudative AMD and have co-existing GA.

The pegcetacoplan group was obtained in reviewing charts from Feb 17, 2023, to March 17, 2024; inclusion criteria were patients who received at least one pegcetacoplan injection and had received their last anti-VEGF injection greater than six months prior to either the time of the chart review or any recurrence that may have occurred while receiving pegcetacoplan injections.

A control group of inactive exudative AMD on PRN anti-VEGF treatment schedules and co-existing GA was identified in reviewing charts between 2019 to 2024 with inclusion criteria of: documented exudative macular degeneration with inactive CNV, documented diagnosis of geographic atrophy, and PRN anti-VEGF therapy. In the control group, exclusion criteria were patients receiving pegcetacoplan injections during the duration of the PRN period, OCT showing evidence of subretinal or intraretinal fluid, as well as patients receiving anti-VEGF injections for diagnoses other than exudative macular degeneration.

Data collected includes age, sex, BCVA at start of PRN therapy, BCVA at start of pegcetacoplan therapy,

reactivation of CNV, and duration of PRN without anti-VEGF.

The primary out come measure calculated was the incidence of recurrent CNV, defined as the reactivation of CNV lesions accompanied by intraretinal or subretinal fluid on OCT and/or leakage on fluorescein angiography (FA) necessitating treatment with anti-VEGF.

Patients that did experience recurrent CNV were switched off of PRN anti-VEGF schedule to a 4 to 8 week anti-VEGF interval, based on the decision making of the treating provider.

Statistical analyses were performed to compare the incidence of recurrent CNV between the pegcetacoplan-treated group and the control group. Statistics were performed utilizing R software and Microsoft Excel and P-values <0.05 were considered significant. Visual acuity was converted from Snellen to LogMAR values as described by Tiew et al[30].

3. Results

The study included 43 exudative AMD patients with co-existing GA who received treatment with pegcetacoplan and maintained a PRN anti-VEGF regimen with inactive CNV for a minimum of 6 months. The control group included 58 exudative AMD patients with co-existing GA who had not received pegcetacoplan and maintained a PRN anti-VEGF regimen with inactive CNV for a minimum of 6 months.

The pegcetacoplan group was 67.4% female with a mean age of 83.9, while the control group was 63.8% female with a mean age of 83.7. At the start of PRN scheduled anti-VEGF injections, the pegcetacoplan group patients had a mean LOGMAR visual acuity of 0.68 (approx. 20/105), while the control patients had a mean LOGMAR visual acuity of 0.94 (approx. 20/174) (p=0.06). At the initiation of pegcetacoplan treatment, the patients had a mean visual acuity of 0.76 (20/115), compared to the start of PRN anti-VEGF treatment (p=0.21).

Table 1. *Baseline Characteristics of Groups. Significance testing for BCVA at 1st Pegcetacoplan compared to Baseline BCVA at PRN anti-VEGF for Pegcetacoplan Group.*

Baseline Characteristics	Pegcetacoplan Group (SD)	Control Group (SD)	p-value
Female	0.674	0.638	
Age	83.86	83.69	
Baseline BCVA at PRN anti-VEGF	0.68(0.52)	0.94(0.79)	0.06
BCVA at 1st Pegcetacoplan	0.76(0.54)		0.21

Among the pegcetacoplan group, the incidence rate was 1.23 (95% CI 0.73, 1.73) recurrences per year for a given patient while receiving pegcetacoplan and not receiving anti-VEGF. The control group had an incidence rate of 0.21 (95% CI 0.11, 0.31) recurrences per year that the patients were not receiving anti-VEGF. The calculated incidence rate ratio of recurrence was 5.891 (p=0.003) for the pegcetacoplan treatment group compared to the control group.

Table 2. *Incidence of Recurrent CNV in Pegcetacoplan and Control Group.*

Primary Outcomes	Pegcetacoplan Group	Control Group	p-value
Incidence (Recurrences/Person-Year)	1.23 (0.73,1.73)	0.21 (0.11,0.31)	0.003

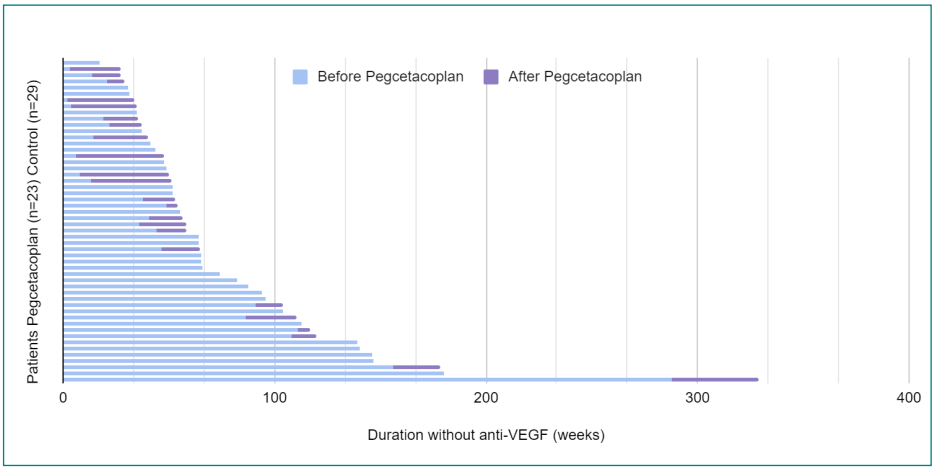

Figure 1. *Duration of PRN before Recurrent CNV. Stacked bars represent patients in the pegcetacoplan group before and after starting pegcetacoplan (n=23). Non-stacked bars represent patients in the control group that never received pegcetacoplan (n=29). Patients that did not have recurrence were excluded.*

4. Discussion

This study demonstrates an increased incidence of recurrent CNV in exudative AMD patients with inactive CNV maintained on a PRN anti-VEGF schedule following pegcetacoplan treatment for GA. These findings suggest that exudative macular degeneration with inactive CNV may be a relative contraindication to pegcetacoplan use and may hasten reactivation of CNV.

Pegcetacoplan is a novel complement inhibitor specifically targeting the alternative complement pathway implicated in the pathogenesis of GA, the advanced dry form of AMD[22,23,25,31]. Specifically, pegcetacoplan targets the complement C3 component, aiming to slow progression of GA by decreasing inflammation and tissue damage promoted through the complement system. While there have been preclinical studies suggesting the proinflammatory downstream effects of the complement system increases angiogenic processes that contribute to CNV formation[32,33], the OAKS and DERBY trials noted increased CNV with pegcetacoplan, which suggests a more complex interaction between complement inhibition and CNV pathogenesis[8,22,27].

A possible explanation for this phenomenon could be related to the role of the complement system in maintaining normal choroidal and retinal homeostasis. While the complement system is implicated in the pathogenesis of AMD through proinflammatory factors, it also plays a role in immune surveillance and the clearance of cellular debris by microglia and monocytes[24,31,34]. Inhibiting complement activity, particularly through a broad inhibitor like pegcetacoplan that targets C3, may disrupt these protective roles, potentially leading to an environment conducive to neovascular growth[34]. The pathogenesis of CNV is thought to involve a complex interplay of molecular and cellular mechanisms, centered on the accumulation of inflammatory debris beneath the RPE and within the choroid, which triggers production of proangiogenic cytokines including VEGF-A[16,35,36]. Dysregulation of cellular mechanisms for maintaining homeostasis and clearance of proinflammatory components that induce oxidative stress may lead to further proangiogenic effects, despite decreasing progression of atrophy from direct tissue damage. This hypothesis is supported by the understanding that complement components, including C3, are involved in regulating angiogenesis. Under normal circumstances complement activation can have both pro-angiogenic and anti-angiogenic effects depending on the context and balance of activation products.

While there was a similar number of reactivation incidents between the two groups, the pegcetacoplan group had a higher rate of reactivation. These inactive patients may have gone on to reactivate without pegcetacoplan, but the data suggests that pegcetacoplan may be decreasing the time patients are able to stay inactive without receiving any anti-VEGF. Patient burden is becoming increasingly important with multiple options for anti-VEGF injections and physicians are increasingly moving toward decreasing injection burden as an important endpoint. While pegcetacoplan has been shown to decrease the rate of GA progression[22,27], it is important to keep in mind this apparent risk of having to restart anti-VEGF injections sooner in this group of patients.

The decision to transition to a PRN anti-VEGF dosing schedule is a complex one for both patients and providers. Often, patients are more comfortable with an extended-duration maintenance schedule of an injection every 3 to 4 months as opposed to PRN. In many cases, the decision is only made once the visual prognosis is sufficiently poor, that the burden of injections is not worth the potential preservation of vision. These patients are often not good candidates for pegcetacoplan either, as their GA has progressed to the point where it involves the fovea and the patients' central vision. These are patients who are at a low risk of recurrent active neovascularization, but who still met criteria for the control group, providing a confounding factor as they represent a different population of patients than those with less advanced GA and inactive previous exudative disease who are receiving pegcetacoplan. Many patients with inactive exudative AMD and GA who were previously monitored and would have been included in the control were then started on pegcetacoplan following its FDA approval. This required the time-separated design that was used. Further study would be warranted with greater sample sizes or more strict criteria to avoid this patient group or analysis of extent of GA and risk of CNV.

Another limitation of the study is its retrospective design. To prove a causal link, a prospective randomized double-blind study would be ideal. The small sample size of our study does limit the results, but as complement inhibitors are further used and

studied for GA, their preferred usage patterns will be further defined as well as real world data on side effects. In particular, studies with longer follow-up on patients receiving pegcetacoplan may be able to better compare incidence and prevalence of reactivated CNV as this study necessitated groups with significantly different durations of follow-up due to the recency of pegcetacoplan's FDA approval. Further study will guide treatment patterns for patients with both exudative macular degeneration and nonexudative macular degeneration with GA.

Previous studies have found increased rates of CNV in eyes with GA in patients with CNV in the fellow eye[37]. While our study did not analyze this in our patients, it would be a promising area of future study in this population in further characterizing the increased risks with pegcetacoplan use.

5. Conclusion

Overall, this study suggests a novel association between patients with inactive prior choroidal neovascularization on PRN scheduling for anti-VEGF injections receiving pegcetacoplan for slowing progression of geographic atrophy and increased incidence of recurrent active exudative choroidal neovascularization requiring anti-VEGF injections. These patients should be closely monitored for signs of recurrent active CNV as they may be at increased risk of recurring sooner, requiring treatment with anti-VEGF intravitreal injections and consideration should be given prior to starting treatment with pegcetacoplan. Further research is needed to elucidate mechanistic links between complement inhibition and CNV pathogenesis and to further define treatment patterns surrounding complement inhibitors for nonexudative macular degeneration with geographic atrophy.

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