LITERATURE REVIEW

REDUCING TREATMENT BURDEN FOR AGE-RELATED MACULAR DEGENERATION PATIENTS: A SYSTEMATIC REVIEW OF RANIBIZUMAB PORT DELIVERY SYSTEM

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ABSTRACT

Introduction: *Ranibizumab port delivery system (R-PDS) is a newly developed method that provides a continuous, long-term supply of ranibizumab into the vitreous, reducing the burden of monthly intravitreal injection visits for neovascular age-related macular degeneration (nAMD) patients. This review aims to evaluate the efficacy and safety of R-PDS in nAMD.*

Methods: *An extensive literature search was performed on 4 online databases: PubMed, Cochrane, ProQuest, and ScienceDirect. The inclusion criteria are human studies comparing R-PDS and intravitreal ranibizumab, English language, with full-text availability. The main outcome measurements are best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters, central foveal thickness (CFT), frequency of treatment, and adverse events.*

Discussion: *Two randomized controlled trials (RCTs) with a total of 635 adults were evaluated. At week 96, R-PDS reported observed mean BCVA changes from baseline (-1.0; +4.2; ETDRS letters) compared to monthly intravitreal ranibizumab (-1.1; +6.1; ETDRS letters). However, there was an increase in mean CFT changes from baseline (+9.9; -15.3 vs −1.3; -21.3, µm) and more severe adverse events frequency (22; 4 vs 4; 0) with R-PDS versus monthly intravitreal ranibizumab, respectively.*

Conclusion: *Ranibizumab PDS showed comparable visual outcomes to intravitreal ranibizumab while demonstrating marginally inferior anatomical outcomes and a higher incidence of severe adverse effects. Despite this, with fewer treatment visits required for up to 24 weeks, R-PDS can potentially reduce the treatment burden in nAMD patients with poor compliance. Further studies are needed to provide better patient eligibility guidelines and recommendations for adverse event management of R-PDS.*

Keywords: *Ranibizumab port delivery system, neovascular age related macular degeneration*

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss among the elderly population worldwide.[1] Over the years, several treatment modalities have been developed to address the neovascular form of AMD, including anti-vascular endothelial growth factor (VEGF) agents. Ranibizumab, a widely used anti-VEGF agent, has

demonstrated significant efficacy in preserving and improving visual acuity in AMD patients. However, monthly intravitreal injections are required for long-term management, posing a significant burden on patients with low compliance and healthcare systems.[2]

In recent years, the development of sustained-release drug delivery systems, such as the ranibizumab port delivery system (R-PDS), has shown promise in reducing treatment burden and improving patient outcomes. The R-PDS is an innovative intravitreal implant that provides a continuous, controlled release of ranibizumab over an extended period. This system eliminates the need for monthly intravitreal injections, potentially improving treatment adherence and reducing the risk of complications associated with repeated injections.[2–4] Several preclinical and clinical studies have evaluated the safety, efficacy, and durability of the R-PDS compared to monthly intravitreal injections of ranibizumab. However, there is a need for a comprehensive analysis comparing the two treatment approaches to provide evidence-based guidance for clinical decision-making.[5]

This study aims to systematically compare the R-PDS and monthly intravitreal injection of ranibizumab in patients with neovascular AMD. By evaluating existing evidence from randomized controlled trials (RCTs), we aim to comprehensively assess the R-PDS as a potential alternative treatment modality for neovascular AMD.

METHODS

Search Strategy and Criteria

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[6] Literature searching was conducted using four online databases (PubMed, ProQuest, the Cochrane Library, and ScienceDirect), and the last search was conducted in March 2023. The search query included port delivery system (port delivery system OR PDS), ranibizumab, AND age-related macular degeneration (age-related macular degeneration OR AMD OR neovascular age macular degeneration OR macular degeneration OR nAMD), including the MESH terms when available, following adaptive search for each database. Search results were imported to Rayyan (rayyan.ai), an artificial intelligence web tool for systematic reviews, where studies were screened for duplicates and processed for study selection.[7]

Eligibility Criteria and Study Selection

The eligible criteria were studies that reported the comparison of ranibizumab port delivery system and monthly intravitreal injection of ranibizumab, with the main outcome measurements of best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy

Score (ETDRS), central foveal thickness (CFT), number of interventions, and safety parameters including adverse events (AE). The studies included are limited to randomized-controlled trial studies published in English with available full-text journal articles. The articles retrieved from the search results were then reviewed independently by four authors (DAAP, AKAP, SHA, JJ) for article eligibility. The risk of bias in the individual studies was assessed using the Cochrane risk of bias tool for randomized trials (Risk of Bias 2.0/ RoB 2.0). Risk of bias assessment was performed at the study level. Disagreements were resolved by discussion and consensus.

Data Extraction

For all eligible studies, data were extracted by two reviewers (DAAP and AKAP), including authors, study methodology, duration of the study, number of subjects, participants' baseline characteristics, intervention characteristics, and follow-ups. Outcomes reported are BCVA, CFT, frequency of treatments, and AE. Data extracted were checked and reviewed by third and fourth reviewers (SHA and JJ).

RESULTS

A preliminary search of the database yielded 408 articles. After duplicate removal with the Rayyan automation tool and additional manual duplicate confirmation, 353 articles were removed through titles and abstracts independent screening by each reviewer without knowing the decisions of other reviewers, and disagreements between reviewers were discussed. Repetitive publications of the same sample were combined, or the most recent was included. Two articles were then selected for final analysis. The details are shown in Figure 1.

Characteristics of the included studies

The two studies included were conducted in the United States. The first study by Khanani et al. is the Ladder trial, a phase 2, multicenter, randomized clinical trial of R-PDS for nAMD of 220 subjects.[3] The second study by Regillo et al. is the Archway trial, a phase 3 randomized controlled, open-label clinical trial of the R-PDS for nAMD of 415 subjects.[4] Both studies selected subjects of 50 years or older with anti-VEGF responsive nAMD proved by improvement of nAMD following anti-VEGF injection prior to trial enrollment and diagnosed within-9 months before study screening. Both studies randomly assigned subjects for receiving treatments with PDS-filled ranibizumab formulation with implant refills or treatments of monthly intravitreal ranibizumab 0.5 mg injections. The outcomes assessed at the end of both studies were (1) efficacy outcomes through (a) BCVA, (b) CFT changes from baseline; (2)

Safety outcomes through ocular and non-ocular AE; and (3) frequency of treatments per patient.

The study by Khanani et al randomized the subjects obtaining R-PDS into three groups of different doses; 10-mg/ml, 40-mg/ml, or 100-mg/ml, while in Regillo et al., subjects received PDS-filled ranibizumab of 100-mg/ml. However, in Khanani et al, when subjects in the R-PDS 10-mg/ml and R-PDS 40-mg/ml treatment arms met a lack of clinical efficacy criteria, they were managed with rescue intravitreal 0.5 mg ranibizumab injection and implant refills with ranibizumab 100-mg/ml formulation. The baseline characteristics were generally well-balanced, as summarized in Table 1.

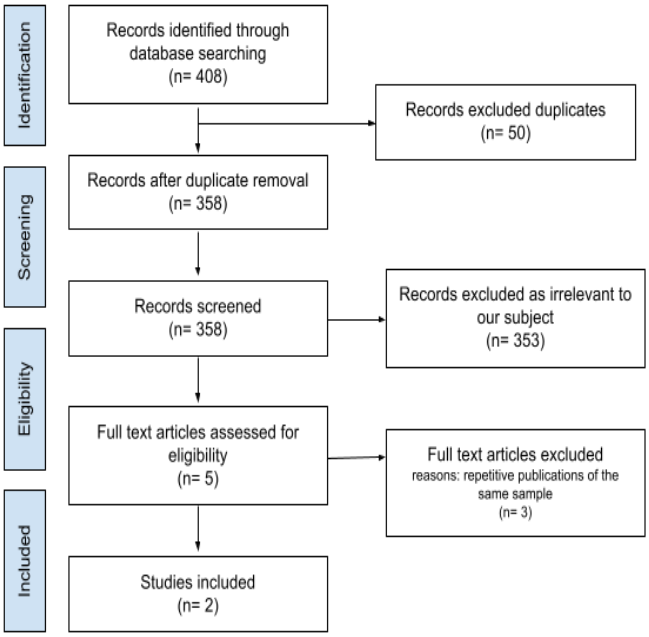

Figure 1. Study flow diagram

Risk of Bias Assessment

In the two included RCTs, the risk of bias results indicates a low risk of bias across all domains, except for domain 3, where some concerns were identified due to the discontinuation of over 10% of subjects in both studies. Notably, both studies excluded several subjects based on reasons such as lack of efficacy and severe AE, thereby highlighting the true value of missing data. As a result of the concerns identified in domain 3, the overall bias assessment for this journal indicates some concerns.

Best-corrected visual acuity (BCVA)

The mean BCVA changes from baseline in two RCTs are documented in Table 2. Consistent similar findings were observed across all studies regarding BCVA changes in patients receiving either PDS or monthly intravitreal ranibizumab treatment. Khanani et al.

reported the highest improvement in BCVA with monthly intravitreal ranibizumab (+6.1), whereas Regillo et al. observed the lowest measurement, a slight decrease of -1.1 ETDRS in the PDS arms.

Table 1. Characteristics of RCTs included

Author (Study)	Year/ Country/ Design	N	I	Dose (n)	Baseline Characteristics							Follow Up (months)
					Age (SD)/ sex (m:f)	Diagnosed time (SD)	Inj. before Study (SD)	BCVA (SD)		CFT (SD)		
Khanani et al (LADDER)[3]	2020/ USA/ Phase 2, multicenter (49 sites) RCT	220	R-PDS	(179) 10mg/ml (58) 40mg/ml (62) 100mg/ml (59)	73.98 (8.4)/ (79:141)	3.5 (1.9)	2.9 (1.3)	70.4 (9.8)	70.0 (11.7)	183.1 (69.2)	186.1 (69.6)	22.1 38
			MIVR	0,5mg (41)				70.6 (12.7)		185.0 (61.6)		21.7
Regillo et al (ARCHWAY)[4]	2023/ USA/ Phase 3, multicenter (78 sites) RCT	415	R-PDS	100mg/ml (248)	75.0 (7.9)/ (245:107)	5.6 (7.4)	5.0 (1.9)	74.4 (10.5)	74.8 (10.4)	176.9 (54.8)	177.0 (52.5)	24 (96 weeks)
			MIVR	0.5mg (167)				75.5 (10.3)		177.2 (49.1)		

N: total patients; I: intervention/ treatment; m: male; f: female; SD: Standard deviation; R-PDS: Ranibizumab Port Delivery System; MIVR: Monthly Intravitreal Ranibizumab.

Table 2. Outcomes Measurements of the RCTs included

Study	I	N	BCVA*	CFT+	F of treatment Mean (SD)	Safety		Discontinuation (%)
						Ocular (%)	Systemic (%)	
Khanani et al. (LADDER)/ 2020[3]	R-PDS 100mg/ml	59	Months 24 4.2 (1.6, 6.9)	[ILM-RPE] –15.3 (–52.0, 21.3) [ILM-Bruch's] +22.3 (-6.8, 51.4)	38 months 2.9 (2.5)	[SAEs][a] 4 (6.8) [AESIs][b] NR [VH] 2 (3.4) [Endophthalmitis] 1 (1.7) [Cataract] 11 (18.6) [Conjunctival Erosion] 1 (1.7)	52 (88.1)	3 (5.1) discontinued before study completion 1 (1.7) adverse event 1 (1.7) death 1 (1.7) lack of efficacy
	MIVR 0.5mg	41	Months 24 6.1 (-0.3, 12.4)	[ILM-RPE] –21.3 (–40.5, –2.2) [ILM-Bruch's] –35.8 (-82.2, 10.7)	38 months 21.9 (8.1)	[SAEs] 0 [AESIs] NR [VH] 0 [Endophthalmitis] 0 [Cataract] 8 (19.5) [Conjunctival Erosion] 0	36 (87.8)	5 (12.2) discontinued before study completion 1 (2.4) death 3 (7.3) withdrawal by patient 1 (2.4) other

Study	I	N	BCVA*	CFT+	F of Treatment Mean (SD)	Safety		Discontinuation (%)
						Ocular (%)	Systemic (%)	
Regillo et al. (ARCHWAY)/ 2023[4]	R-PDS 100mg/ml	248	Weeks 96 -1.1 Observed BCVA 73.4 (SE, 13.28)	[ILM-RPE] +9.9 (SE, 3.64)	96 weeks 4.1 (0.8)	[SAEs] 22 (8.9) [AESIs] 59 (23.8) [VH] 15 (6.0) [Endophthalmitis] 4 (1.6) [Cataract] 22 (8.9) [Conjunctival Erosion] 10 (4.0)	61 (24.6)	24 (9.7) discontinued before study completion 10 (4.0) adverse events 7 (2.8) death 3 (1.2) lost to follow-up 1 (0.4) noncompliance with study drug 1 (0.4) withdrawal by patient 2 (0.8) other
	MIVR 0.5mg	167	Weeks 96 -1.0 Observed BCVA 74.4 (SE, 14.47)	[ILM-RPE] -1.3 (SE, 4.48)	96 weeks 22.9 (3.8)	[SAEs] 4 (2.4) [AESIs] 17 (10.2) [VH] 6 (3.6) [Endophthalmitis] 1 (0.6) [Cataract] 10 (6.0) [Conjunctival Erosion] 0	36 (21.6)	13 (7.8) discontinued before study completion 1 (0.6) adverse event 4 (2.4) death 7 (4.2) withdrawal by patient 1 (0.6) physician decision

I: Intervention; SD: Standard deviation; N= number of samples; F: frequency; VH: Vitreous Hemorrhage; NR: Not Reported; ILM (Inner Limiting Membrane); RPE (Retinal Pigment Epithelium).

*Mean BCVA Change from Baseline (ETDRS Letters)

+Mean CFT Changes from Baseline (μm (95 %CI))

[a]SAEs = Serious Adverse Events. SAEs reported consist of vitreous hemorrhage, endophthalmitis, retinal hemorrhage, reduced visual acuity, and other events.

[b]AESIs = Adverse Event of Special Interests (n= patients with ≥ 1 AESIs). AESI were chosen and prespecified based on safety data from the Ladder phase 2 trial to report specific events of interest promptly for the safety profile of the PDS and its procedures. AESI in this study referred to as vitreous hemorrhage, endophthalmitis, retinal detachment, conjunctival retraction, conjunctival erosion, conjunctival bleb or conjunctival filtering bleb leak, hyphema, and cataract.[4]

Table 3. Ocular Adverse Events

Study	Events	R-PDS 100mg/ml [n,(%)]		M-IVR 0.5mg [n,(%)]	
		<1mo	>1 mo	<1 mo	>1 mo
Khanani et al. (LADDER)/ 2020[3]	AE	50 (84.7)	35 (59.3)	4 (9.8)	26 (63.4)
	SAE	3 (5.1)	2 (3.4)	0	0
	VH_1	3/5 (60.0)	0	NR	
	VH_2	2/54 (5.6)	0	NR	
Regillo et al. (ARCHWAY)/ 2023[4]	AE	228 (91.9)	150 (60.5)	18 (10.8)	82 (49.1)
	SAE	8 (3.2)	15 (6.0)	1 (0.6)	3 (1.8)
	VH	12/248 (4.8)	3/248 (1.2)	6 (3.6)	

n: number of patients; mo: months; AE: adverse events; SAE: serious adverse events; VH_1: Vitreous hemorrhage before procedure update; VH_2: Vitreous hemorrhage after procedure update; NR: Not Reported

Central foveal thickness (CFT)

The mean CFT changes from baseline in 96 weeks were summarized in Table 2. Khanani et al. reported the mean CFT change from baseline in 96 weeks was -15.3 µm in the R-PDS 100 mg/mL and -21.3 µm in the monthly intravitreal ranibizumab 0,5 mg arm, with mean baseline CFT being 186.1 µm in all patients.

Regillo et al. reported similar results in the mean change from baseline in CFT, which were +9.9 µm (SE, 3.64 µm) and -1.3 µm (SE, 4.48 µm) in the R-PDS and monthly ranibizumab arms, respectively, with mean baseline CFT was 176.9 µm ± 54.8 µm in the ranibizumab PDS and 177.2 µm ± 49.1 µm in the monthly intravitreal ranibizumab arm.

Frequency of treatments

The mean frequency of treatments per patient in two distinct studies is presented in Table 2. The findings from both studies indicate that R-PDS required fewer treatments than intravitreal ranibizumab. Specifically, Khanani et al. reported a mean of 2.9 treatments for R-PDS and 21.9 for intravitreal ranibizumab, compared to Regillo et al. found a mean of 4.1 treatments for R-PDS and 22.9 for intravitreal ranibizumab. It is important to note that these studies were conducted during different periods due to limited data availability.

Safety outcomes

As observed in both studies, ocular AE was reported more frequently in R-PDS than in the monthly intravitreal ranibizumab, specifically during the "postoperative period", defined as up to 37 days after implant insertion. The number of AE dropped in the ranibizumab PDS arm >1 month (after "postoperative period") compared to <1 month ("postoperative period"), as shown in Table 3.

Khanani et al. described a significant number of postoperative vitreous hemorrhage AE originating from the pars plana in the first 22 patients treated with the original implant insertion technique from the start of the study. This procedure was then optimized to improve safety,

resulting in a notable decrease in vitreous hemorrhage incidence throughout the study, as shown in Table 3. To manage PDS-related AE, 25/179 PDS patients required extra surgical intervention. Eleven of these patients were among the 22 who operated before the implant insertion method was optimized. The remaining 14/157 patients were implanted following procedure optimization.

Vitreous hemorrhage and endophthalmitis are reported as the most frequent and notable serious adverse events (SAE). Most cases of vitreous hemorrhage were classified as mild to moderate intensity in both studies. For all cases of endophthalmitis found in Khanani et al., culture results were negative.[2] Additionally, Regillo et al. reported no cases of endophthalmitis were considered to be related to the refill-exchange procedure. The most prevalent Adverse Event of Special Interest (AESI) documented are cataracts and conjunctival erosion. Regillo et al also identified the number of patients with ocular AESI who require additional procedures was 21/59 (35.6%) and 3/17 (17.6%) in Ranibizumab PDS and monthly ranibizumab arm, respectively. The majority of procedures in the R-PDS arm are conjunctival repair or cataracts.

All included studies identified no patterns or trends in the reported cause of death and causal relationship with the given treatment. It can be concluded that no systemic serious AE and deaths of patients were considered by study investigators to be related to the study treatment.

DISCUSSION

Vukicevic et al. proposed that frequent administration of anti-VEGF injections imposes a substantial burden on patients, caregivers, and healthcare providers.[8] Conversely, the successful treatment of R-PDS in both studies effectively diminished the overall treatment burden for patients. R-PDS patients, during the time of analysis, received approximately 80% fewer ranibizumab treatments compared to patients receiving monthly intravitreal ranibizumab 0.5-mg injections.

In one study (Khanani et al.), visual and anatomical outcomes at month 9 were similar between R-PDS patients and those receiving monthly intravitreal ranibizumab, indicating that clinical effectiveness need not be compromised to reduce the treatment burden. These findings collectively propose that R-PDS represents a promising approach to alter the treatment paradigm for nAMD and address the existing unmet need for reducing treatment burden while upholding or enhancing patient outcomes. However, Regillo et al. reported a slightly inferior anatomical outcome despite comparable visual outcomes.

An improvement in BCVA was observed in the Khanani et al. study. In 96 weeks, both the R-PDS 100mg/ml group and the monthly intravitreal 0.5mg ranibizumab group demonstrated improvement in BCVA (+4.2 and +6.1, respectively). Interestingly, although both Regillo et al. and Khanani et al. use R-PDS 100mg/ml, one study showed BCVA improvement (+4.2 ETDRS), while the other did not (-1.1 ETDRS). It's worth noting that all patients included in both studies had received anti-VEGF treatment prior to trial and had shown positive responses to the treatment. Therefore, achieving significant vision gains was not the primary objective, as indicated by the relatively high baseline BCVA scores of 70.0 and 74.8 ETDRS in both studies. R-PDS treatment was given to maintain visual acuity over time. As seen in Table 2, both studies have similar results in terms of maintaining BCVA.

In both studies, anatomic outcomes were assessed by evaluating CFT from baseline status**,** measured from the internal limiting membrane (ILM) to the retinal pigment epithelium (RPE). The mean CFT change from baseline was different between the two studies, in the R-PDS in week 96 (-15.3, 9.9 µm) compared to a decrease of mean CFT change from baseline in subjects receiving monthly intravitreal ranibizumab (-21.3, -1.3 µm). However, Sugar et al. reported in patients with macular edema, the threshold for changes in CFT that cause clinically significant changes in visual acuity is 20% from baseline.[9] The study reported in eyes with an improvement in visual acuity greater than five letters; there was a decrease in retinal thickness of 20% or greater.

Both studies reported that the mean CFT change to baseline remained consistent throughout the study. In Khanani et al, an additional measurement of CFT was assessed from the ILM to Bruch's membrane to include pigment epithelial detachment (PED) height. The mean CFT change to baseline measured from ILM to Bruch's membrane on week 96 were different between the R-PDS and monthly ranibizumab intravitreal (+22.3, -35.8 µm); yet, the mean CFT change also remained stable until the final follow-up of 38 months. Regillo et al. reported a tendency for CFT to increase before each refill-exchange procedure, with an average change of approximately 10 µm. However, following each refill exchange procedure, CFT tended to decrease and return to baseline levels.

This review demonstrated more AE incidence in the R-PDS arms compared to the monthly ranibizumab arm, which was anticipated due to the insertion surgery procedure. Adverse event data were greatly influenced by the postoperative period and insertion method used. The rate of patients experiencing ocular AESIs after the first refill-exchange interval was comparable in R-PDS patients and monthly ranibizumab patients, showing that the initial surgery had a significant impact on the safety profile of R-PDS.

Vitreous hemorrhage incidents originating from the pars plana dropped significantly after the modified procedure. Most cases of endophthalmitis in the Archway trial are also related to cases of conjunctival erosion or retraction. This demonstrates the importance of conjunctival and Tenon's capsule integrity at the implant insertion site.[2] A decrease in complication rates and better results are expected as surgeons acquire expertise doing new surgery methods following a learning curve.[10] Endophthalmitis incidences observed in this review are similar to other ocular implants, such as glaucoma drainage devices, ranging from 0.5% to 1.6% in clinical trials,[11] and for intravitreal injections (0.4-1.5%).[12] Additionally, one study also reported that the cumulative rate of endophthalmitis increased from 0.055% after the 10th injection to 0.843% after the 60th injection.[13]

Complications related to R-PDS were generally manageable and rarely led to severe, irreversible vision loss. Established through Ladder and Archway clinical trials, strategies for the management of key ocular AE that may be encountered with R-PDS are provided in a study by Awh et al.[14] Management including interruption of ranibizumab refill dose, implant saline flush, early identification through diagnostic workup, culture, and treatment with pharmacological and surgical intervention if considered necessary. A training tool using virtual reality has been developed for PDS and is accessible to surgeons undergoing PDS surgical training.[15] Furthermore, the importance of careful patient selection early in therapy, in terms of conjunctival, scleral, and other ocular surface health status, may support the success and long-term outcome of R-PDS.[14]

According to a study by Chang et al, overall treatment satisfaction scores assessed with the Macular Disease Treatment Satisfaction Questionnaire were slightly better for the R-PDS compared to intravitreal injection arms (mean 68.0; 95% CI, 67.4-68.6; n = 237 and mean, 66.1; 95% CI, 64.9-67.3; n = 159, respectively). Despite the fact that R-PDS patients had greater AE, nAMD therapy with R-PDS was strongly preferred above standard-of-care intravitreal injections by 93.2% of R-PDS patients.[16]

LIMITATIONS

This study has several limitations to consider. Due to the novelty of the R-PDS, there is a limited number of studies available for review. The samples evaluated in the existing studies are limited to patients who are responsive to anti-VEGF treatment, potentially impacting the generalizability of the findings. Longer follow-up periods are necessary to assess the durability and potential late-stage complications associated with the R-PDS.

CONCLUSION

The visual and anatomical outcomes of R-PDS were found to be similar to monthly intravitreal ranibizumab. Although a higher occurrence of severe adverse effects is reported, these complications were generally manageable and rarely led to irreversible impairment or vision loss. Moreover, R-PDS is a favorable option for patients with low compliance, healthy conjunctiva, and Tenon's capsule integrity due to the reduced number of injections needed. Further investigations are warranted to establish improved guidelines for R-PDS patient eligibility, updated instructions and recommendations for the R-PDS related procedure, and AE management.

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