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Guideline & Consensus

Chinese Guideline for the Management of Polypoidal Choroidal Vasculopathy (2022)

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Abstract

Background In mainland China, patients with neovascular age-related macular degeneration (nAMD) have an approximately 40% prevalence of polypoidal choroidal vasculopathy (PCV). This disease leads to polys, recurrent retinal pigment epithelium detachment (PED), extensive subretinal or vitreous hemorrhages, and severe vision loss. China has introduced various treatment modalities in the past years, and gaining comprehensive experience in treating PCV is necessary.

Methods A total of 14 retinal specialists nationwide with expertise in PCV were empaneled to prioritize six questions and address their corresponding outcomes, regarding opinions on inactive PCV, choices of anti-vascular endothelial growth factor (anti-VEGF) monotherapy, photodynamic therapy (PDT) monotherapy or combined therapy, patients with persistent subretinal fluid (SRF) or intraretinal fluid (IRF) after loading dose anti-VEGF, or patients with massive subretinal hemorrhage. An evidence synthesis team conducted systematic reviews, which informed the recommendations that address these questions. This guideline used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach to assess the evidence's certainty and grade the recommendations' strengths.

Results The panel proposed the following six conditional recommendations regarding treatment choices: (1) For patients with inactive PCV, we suggest observation over treatment; (2) For treatment-naïve PCV patients, we suggest either anti-VEGF monotherapy or combined anti-VEGF and PDT rather than PDT monotherapy; (3) For patients with PCV who plan to initiate combined anti-VEGF and PDT treatment, we suggest later/rescue PDT over initiate PDT; (4) For PCV patients who plan to initiate anti-VEGF monotherapy, we suggest treat and extend (T&E) rather than the pro re nata (PRN) regimen following three monthly loading doses; (5) For patients with persistent SRF or IRF on optical coherence tomography (OCT) after three monthly loading doses, we suggest proceeding with anti-VEGF treatment rather than observation. (6) For PCV patients with massive subretinal hemorrhage (equal to or more than four papillary diameters) involving the central macula, we suggest surgery (consider using a complementary therapy, e.g., pneumatic displacement, anti-VEGF, PDT, tissue-Plasminogen Activator [t-PA]) rather than anti-VEGF monotherapy.

Conclusions: Six evidence-based recommendations support optimal care for PCV patients' management.

Keywords: polypoidal choroidal vasculopathy; anti-vascular endothelial growth factor; photodynamic therapy; surgery
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Box 1: Summary of Recommendations	
1	For treatment-naïve polypoidal choroidal vasculopathy (PCV) patients with inactive polypoidal lesions, the guideline panel suggests observation over the initiation of treatment (Conditional recommendation, very low certainty in the estimated effects).
	Remarks: Close follow-up and monitoring are essential, especially for patients with high-risk factors (such as cigarette smoking, higher body mass index, and abnormal serum levels of inflammatory markers).
2	For treatment-naïve PCV patients, the guideline panel suggests either anti-VEGF monotherapy or combined anti-VEGF and PDT rather than PDT monotherapy (Conditional recommendation, low to very low certainty in the estimated effects).
	Remarks: The choice may depend on the patient's condition (such as the size or location of polypoidal lesions and the height of PED) or specific types of anti-VEGF agents.
3	For PCV patients who plan to initiate anti-VEGF combined with PDT treatment, the guideline panel suggests later/rescue PDT over initial PDT (Conditional recommendation, low certainty in the estimated effects).
	Remarks: The timing of later PDT may be at least after three months of anti-VEGF according to treatment criteria of PDT (such as if polypoidal lesions were seen with subretinal fluid on the ICGA images obtained)
4	For PCV patients who plan to initiate the treatment with anti-VEGF, the guideline panel suggests treat and extend (T&E) over the pro re nata (PRN) regimen following three monthly loading doses (Conditional recommendation, very low certainty in the estimated effects).
	Remarks: The T&E regimen increases the number of injections compared to the PRN regimen, although it reduces the number of visits. The follow-up should consider the morphological changes of the fundus and pay more attention to the functional or conscious symptoms of the affected eye. The interval of T&E could be referred to in the ALTAIR study.
5	For PCV patients with persistent subretinal fluid (SRF) or intraretinal fluid (IRF) on optical coherence tomography (OCT) after three monthly anti-VEGF treatments, the guideline panel suggests proceeding with anti-VEGF treatment over observation (Conditional recommendation, very low certainty of the estimated effects).
	Remarks: Clinicians should closely monitor the change in fundus morphology and function of the affected eye (or subjective symptoms) during follow-up and could consider stopping treatment when no clear benefit to visual acuity with further injection is expected, such as extensive subretinal scar formation.
6	For PCV patients with massive subretinal hemorrhage (equal or more than four papillary diameters) involving the central macula within the onset of 14 days, the panel suggests vitrectomy in combination with rtPA intraocular injection and gas tamponade over anti-VEGF monotherapy (Conditional recommendation, very low certainty in the estimated effects).
	Remarks: Surgery may also benefit PCV patients with subretinal hemorrhage combined with vitreous hemorrhage; clinicians might consider using complementary therapy (e.g., pneumatic displacement, anti-VEGF, PDT, tissue-Plasminogen Activator [t-PA]).

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INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is a variant of type 1 macular neovascularization (MNV[1,2], which manifests as macular edema, pigment epithelial detachment (PED), submascular hemorrhage, and even hemorrhagic retinal detachment and vitreous hemorrhage, leading to severe vision loss[3]. Studies showed that patients with neovascular age-related macular degeneration (nAMD) in mainland China have a high prevalence of PCV (40% approximately)[4,5].

Multiple model fundus imaging has been used in clinical practice to diagnose PCV. Fundus photography detects orange nodules, extensive subretinal hemorrhages, hemorrhagic PED, etc. The double-layer sign and notched or peaked PED, pachychoroid are observed under optical coherence tomography (OCT)[6]. Usually, a PCV lesion demonstrates the characteristics of occult choroidal neovascularization (CNV) on fluorescein angiography (FA). Polypoidal lesions or branching vascular networks (BVN) are identified by indocyanine green angiography (ICGA), the gold standard for diagnosing PCV[7]. Optical coherence tomography angiography (OCTA) is also used to diagnose PCV during patient follow-up. Tangled vascular structure of BVN and polypoidal lesions are identified with OCTA imaging[8,9].

The current treatment choices for PCV are laser photocoagulation, photodynamic therapy (PDT), intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, or surgery. Because active polypoidal lesions can potentially lead to hemorrhage or vision loss, the primary treatment goal has been modified. It aims to achieve the best visual outcome and minimize the treatment burden[7,10,11].

Although various treatment options exist, especially considering the significant heterogeneity in clinical presentation, determining the optimal timing and the best treatment choices remain challenging. Few evidence-based clinical practice guidelines for PCV patients have focused on comprehensive treatment strategies. Considering China's high PCV prevalence, we invited a national PCV specialist panel from the Chinese Retina Society to develop this evidence-based guideline.

METHODS

Guideline Scope and Target Audience

Despite the limited number of randomized controlled trials (RCTs) evaluating PCV, we sought to develop an evidence-based guideline focusing on PCV's treatment. This guideline is intended to promote patient-centered care and improve patient-benefited outcomes (*e.g.*, improvement in visual acuity, reduction in visits or treatments). This guideline will also potentially provide information for policymakers to eye healthcare decision-making.

The guideline aimed to address (1) the management strategy for patients with inactive polypoidal lesions; (2) the optimal intervention(s) for active PCV patients who plan to initiate treatment; (3) the optimal timing to introduce PDT when combined with anti-VEGF treatment; (4) the optimal regimen of injections when using anti-VEGF treatment; (5) the treatment strategy for patients undergoing the initial anti-VEGF monotherapy with persistent SRF or IRF on OCT after three monthly

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anti-VEGF treatments; (6) the optimal treatment for patients with massive subretinal hemorrhage and involving the central macula (**Figure 1**).

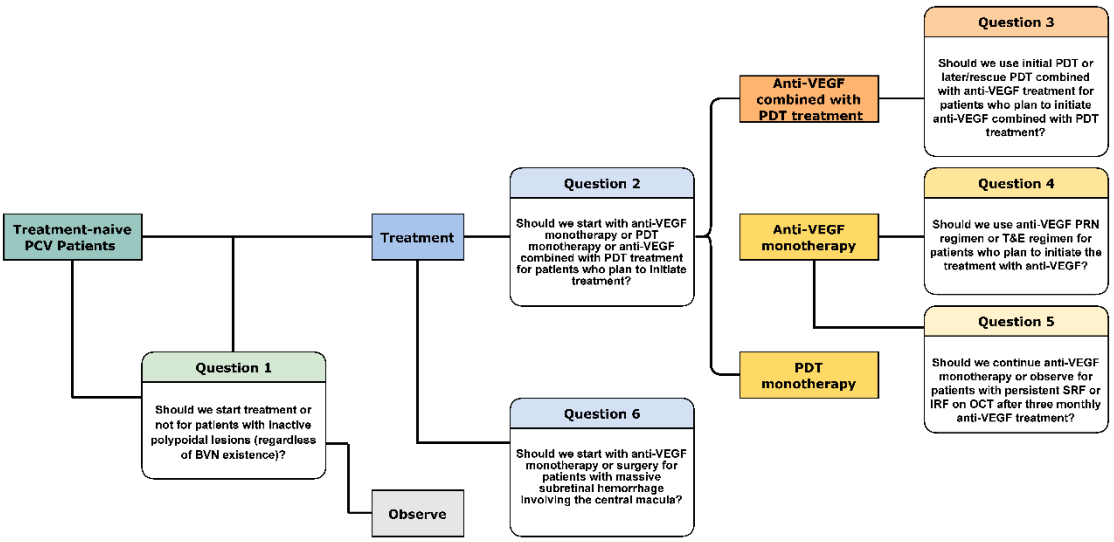

Figure 1. Logic model for identification of important clinical questions on clinical management of PCV.

Notes: VEGF: vascular endothelial growth factor; BVN: branching vascular network; IRF: intraretinal fluid; PCV: polypoidal choroidal vasculopathy; PDT: photodynamic therapy; PRN: pro re nata; SRF: subretinal fluid; T&E: treat and extend.

Guideline Development and Review Process

The methods employed in developing this ophthalmic guideline are in strict accordance with the principles of credible evidence-based clinical guidelines proposed by the National Institute of Health[12]. The GRADE (grades of recommendations assessment, development, and evaluation) approach was used to rate the certainty of evidence and the strength of recommendations[13-16].

Panel Composition

The Chinese Retina Society organized a panel consisted of a methodologist (Zhang YQ) and 14 top retinal experts who are specialized in PCV from 13 hospitals in nine provinces (Beijing, Hunan, Sichuan, Liaoning, Guangdong, Shanghai, Hubei, Shaanxi, Jiangsu) across China.

Conflict-of-Interest Management

All panel members' potential personal conflicts of interest (including financial and professional-related conflicts) were collected. Most members (72%) were determined to have no substantial conflict of interest. The remaining members (28%) stated that they have participated in corporate-sponsored research or been invited by corporations as speakers and the conflict was not severe enough. Hence, all panels experienced the discussion and formulated the recommendations.

Questions and outcomes of interest

Six clinical questions were framed in PICO (Population, Intervention, Comparator, Outcomes) format. Through two rounds of an online survey (developed by Wenjuanxing, https://www.wjx.cn), all panel members participated in the questions generation and modification and confirmed the

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questions to be included in this guideline. The panel defined and selected outcomes for all included clinical questions as a priority and rated the importance of the outcomes using a 9-point scale (7 to 9 for critical outcomes, 4 to 6 for important outcomes, and 1 to 3 for unimportant outcomes) through an online survey. The panel identified the critically important outcomes for all questions as follows: (1) best-corrected visual acuity (BCVA) changes as measured by the mean change from baseline in the number of letters of BCVA at one year or longer; (2) the proportion of participants who lost 15 or more letters in BCVA at one year or longer. The panel also identified other important outcomes for all questions as follows: (1) lesion progression at one year or longer; (2) the proportion of participants who gained 15 or more letters in BCVA at 1 year or longer; (3) the absence of edema on OCT at 1 year; (4) the regression rate for polypoidal lesions observed by ICGA at 1 year or longer; (5) number of treatments at 1 year; (6) the number of doctor visits at 1 year; (7) the incidence of all systemic severe adverse events at 1 year or longer; (8) the incidence of ocular severe adverse events (including endophthalmitis, retinal pigment epithelial tears, anterior chamber inflammation, increased intraocular pressure, and intraocular hemorrhage) at 1 year or longer; (9) quality of life assessed by a valid scale (*e.g.*, National Eye Institute Visual Function Questionnaire [NEI-VFQ]) at 1 year or longer; (10) incidence of thrombosis events at 1 year or longer. A thrombosis event is defined as the occurrence of any of the following: (A) myocardial infarction; (B) nonhemorrhagic stroke; (C) angina; (D) ischemic heart disease; (E) thrombosis; and (F) death from cardiovascular disease.

Literature search

Two bioinformatics specialists (Schoones J and Shao SM) worked with the methodologist (Zhang YQ) and the evidence synthesis team (Qi F and Zhang Y) to develop the search strategy. Nine Chinese and English databases, including MEDLINE, EMBASE, Cochrane Library, Web of Science, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Data, and China Science and Technology Journal Database (VIP), were searched from inception to November 29th, 2019, and updated in October 2021. In addition to the database search, the included studies in relevant systematic reviews were checked, and panel members provided additional critical studies. Detailed search strategies were presented in the **supplementary**.

Literature screening and evidence synthesis

Two systematic reviewers independently screened identified articles (according to the abstract and the full text) and extracted data from eligible studies. The PRISMA flow diagram for all PICO questions was presented in the **Supplementary**. A third reviewer assisted in resolving any disagreement. Inclusion, exclusion criteria, and data extraction tables (Excel) were developed in advance.

Randomized controlled trials (RCTs) were prioritized for inclusion for each clinical question. When RCT evidence was lacking, indirect, non-randomized controlled studies or noncomparative evidence were included. The Cochrane bias risk assessment tool[17] was used to evaluate the risk of bias of included RCTs. The Newcastle-Ottawa Scale (NOS)[18] was employed to assess the risk of bias of included comparative observational studies. The National Institutes of Health (NIH) (https://wwwnhlbinihgov/health-topics/study-quality-assessment-tools) bias risk assessment tool

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for before-after (pre-post) studies was used to evaluate the risk of bias of the included uncontrolled studies.

RevMan 5.3 software was employed for the RCTs and observational studies, and a random-effects model was used for meta-analysis[19]. Risk ratios (RRs) and their 95% confidence intervals (*CI*s) were estimated for dichotomous outcomes. Mean differences (MDs) and their 95% *CI*s were calculated for continuous outcomes. For noncomparative studies (single-arm data), R software version 4.0.2 (meta-package, the R Core Team 2020) was used to combine data using a random-effects model, where the incidence and its 95% *CI* were combined for dichotomous outcomes, and changes in data before and after treatment and their 95% *CI* were combined for continuous outcomes. Before meta-analysis, to fully consider the clinical and methodological heterogeneity across studies, a descriptive analysis was conducted for results that could not be combined. The chi-square test and I^2 statistics were used to evaluate statistical heterogeneity. When the Chi-square test was P <0.1 and I^2 >50%, statistical heterogeneity was considered[17]. When statistical heterogeneity was identified, a subgroup analysis was conducted to explore the source of heterogeneity based on the following factors: drug type, follow-up time, initial treatment or not, and drug treatment frequency. When subgroup differences were identified, the results were reported separately according to the different levels of that factor.

The GRADE approach was used to assess the certainty (very low, low, moderate, and high) of the evidence[14,20]. We also systematically reviewed the evidence about patient values and preferences, cost-effectiveness, health equity, acceptability, and feasibility. For the evidence summary and presentation of each clinical question, we used the GRADEpro guideline development tool (www.gradepro.org) to construct a GRADE evidence summary and an evidence-to-decision (EtD) framework to assist the decision-making process[13,16].

Formulating Recommendations

Panel members reviewed the evidence profile and EtD tables before the two video conferences on September 26th and 27th, 2020. Panel members formulated the recommendations after assessing the benefits and harms, certainty in the effect estimate, patient values and preferences, resource usage, feasibility, acceptability, and equity of the alternative care options. The GRADE approach was used to decide the strength of the recommendations. All panel members reached a consensus regarding the direction and strength of the recommendation, along with the corresponding remarks through discussion and voting. All opposing opinions and rationales were recorded on the EtDs to keep the decision-making process transparent.

QUESTIONS AND RECOMMENDATIONS

Question 1 For treatment-naive PCV patients with inactive polypoidal lesions (regardless of BVN existence), should observation or initiation of treatment be implemented?

(Active: subretinal fluid, intraretinal fluid, subretinal hemorrhage, PED on OCT or vitreous hemorrhage. Inactive: without above lesions)

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Recommendation 1 For treatment-naive PCV patients with inactive polypoidal lesions (regardless of BVN existence), the guideline panel suggests observation over the initiation of treatment

(conditional recommendation, very low certainty in the estimated effects).

Remarks: Close follow-up and monitoring are essential, especially for patients with high-risk factors[21-23] (such as cigarette smoking[24], higher body mass index[25]), and abnormal serum levels of inflammatory markers[26,27]).

Summary of the evidence

Only two non-comparative studies were identified that addressed this question[28,29]. The EtD framework is shown in **Supplementary Table 1**.

Benefits and harms

The only evidence on non-treated PCV patients with inactive polypoidal lesions was identified. Two patients[29] (three eyes) were followed up for 10–29 months without significant BCVA changes from baseline, and none of the three eyes showed lesion progression. The other patient[28] was followed up for 69 months, BCVA decreased three letters from baseline, and one eye showed lesion regression despite shallow serous detachment of the neurosensory retina around the nodules that appeared and resolved repeatedly, no severe subretinal hemorrhage, hard exudates or severe ocular adverse events occurred during the follow-up period[28].

Certainty of the evidence

All the critical outcomes (the mean change from baseline in the number of letters of BCVA, lesion progression, and incidence of ocular severe adverse events) were of very low certainty of evidence. Therefore, the overall certainty of the evidence was very low.

Other considerations

Despite the lack of evidence supporting immediate initiation of treatment, visual loss, and lesion progression in patients under observation were trivial, with negligible adverse events (very low certainty). Patient values and preferences may not be subject to significant uncertainty or variability.

Panel discussion and conclusions

The observation could lead to moderate savings in medical resources. Observation could also be accepted by patients and clinicians and easily implemented. Follow-ups of the patients for the status of polypoidal lesions are essential at no more than three months, especially for patients with high-risk factors (such as cigarette smoking[24], higher body mass index[25], abnormal serum levels of inflammatory markers[26,27]). Patients are suggested to use the Amsler grid for self-monitoring at home and to see ophthalmologists when new abnormal signs are detected.

Question 2 For PCV patients who plan to initiate treatment, should we start with anti-VEGF monotherapy, PDT monotherapy, or anti-VEGF combined with PDT treatment?

Recommendation 2 For PCV patients who plan to initiate treatment, the guideline panel suggests either anti-VEGF monotherapy or combined anti-VEGF and PDT rather than PDT monotherapy

(conditional recommendation, low to very low certainty in the estimated effects).

Remarks: The choice may depend on the patient's condition (such as the size or location of polypoidal lesions and the height of PED) or specific types of anti-VEGF agents.

Question 2.1 For PCV patients who plan to initiate treatment, should we start with anti-VEGF

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monotherapy or PDT monotherapy?

Recommendation 2.1 For PCV patients who plan to initiate treatment, the guideline panel suggests starting with anti-VEGF monotherapy over PDT monotherapy (conditional recommendation, very low certainty in the estimated effects).

Summary of the evidence

A total of five RCTs were identified that addressed this question[30-34]. The EtD framework is shown in **Supplementary Table 2**.

Benefits and harms

Compared with PDT, patients receiving mono anti-VEGF treatment were likely to have a slight mean increase of 2.5 BCVA letters per year from baseline (*n* = 218; MD, 2.5 [95% *CI*, 1 to 4]; moderate certainty)[30-34]; the proportion of patients with BCVA increased by 15 or more letters may be increased by 75% (*n* = 42; RR, 1.75 [95% *CI*, 0.6 to 5.10]; absolute risk ratio (ARR), an increase of 143 cases per 1000 population [95% *CI*, a decrease of 76 cases per 1000 population and a rise of 781 cases per 1000 population]; very low the observation. The regression rate of polypoidal lesions in patients receiving mono anti-VEGF treatment may be reduced by 50% (*n* = 83; RR= 0.50 [95% *CI*, 0.32 to 0.78]; ARR, a decrease of 375 cases per 1000 population [95% *CI*, a reduction of 510 cases per 1000 population and a drop of 165 cases per 1000 population]; low certainty[30,34]). Patients receiving mono anti-VEGF treatment may slightly increase by 2.18 times in the average number of treatments within one year (*n* = 59; MD= 2.18 [95% *CI*, 1.18 to 2.55]; low certainty[32,34]). There was probably little difference between mono anti-VEGF and PDT in the incidence of ocular severe adverse events (*n* = 41; RR= 1.28 [95% *CI*, 0.09 to 19.06]; ARR, an increase of 12 cases per 1000 population [95% *CI*, a decrease of 40 cases per 1000 population and a rise of 785 cases per 1000 population]; low certainty[34]).

Certainty of the evidence of effects

The critical outcomes contributing to this recommendation (the proportion of patients with BCVA that increased or decreased by 15 or more letters) were of very low certainty of evidence. Therefore, the overall certainty of the evidence was very low.

Other considerations

Since most patients prefer visual improvement to the burden of increased treatment sessions, mono anti-VEGF treatment was superior to PDT. Similarly, mono anti-VEGF treatment may lead to moderate medical cost savings in the Chinese setting as it is covered by national medical insurance and is more directly cost-effective than PDT[34].

Panel discussion and conclusions

Anti-VEGF monotherapy may increase health equity and can be accepted and easily implemented by key stakeholders.

Question 2.2 For PCV patients who plan to initiate treatment, should we start with anti-VEGF monotherapy or anti-VEGF combined with PDT treatment?

Recommendation For PCV patients who plan to initiate treatment, the guideline panel suggests starting with either anti-VEGF monotherapy treatment or anti-VEGF combined with PDT treatment over PDT monotherapy (conditional recommendation, low certainty in the estimated

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effects).

Remarks: The choice may depend on the patient's condition (such as the size or location of polypoidal lesions and the height of PED) or specific types of anti-VEGF agents.

Summary of the evidence

A total of nine RCTs were identified addressing this question[30,32-40]. Six studies[30,32-34,37,40] evaluated ranibizumab, two studies[35],[36] evaluated aflibercept, and one study[38] evaluated bevacizumab. The EtD framework is shown in **Supplementary Table 3**. No eligible RCT investigated conbercept for this question, and descriptive results on non-comparative studies on conbercept were investigated and presented in the discussion section.

Benefits and Harms

Compared with anti-VEGF combined with PDT treatment, anti-VEGF monotherapy may reduce the proportion of patients with a reduction in BCVA by 15 or more letters (n = 41 [although the study included a sample size of 318, the number of patients who were actually eligible and randomized to both arms of combined PDT treatment was only 41]; RR= 0.82 [95% *CI*, 0.22 to 3.00]; ARR, six cases per 1000 [95% *CI,* a decrease of 24 cases per 1000 and an increase of 62 cases per 1000]; low certainty; see Supplementary Table 3 for more details)[35]. There may be little difference between anti-VEGF monotherapy and anti-VEGF combined with PDT treatment in terms of the risk of serious ocular adverse events (*n* = 396; *RR*= 0.76 [95% *CI*, 0.09 to 6.27]; ARR, a decrease of five cases per 1000 [95% *CI*, a reduction of 18 cases per 1000 and an increase of 106 cases per 1000]; low certainty)[34,35,37]. The incidence of arteriothrombotic events was likely to be little difference between anti-VEGF monotherapy and anti-VEGF combined PDT treatment (*n* = 75; *RR*= 0.60 [95% *CI*, 0.08 to 4.75]; ARR, a decrease of five cases per 1000 [95% *CI*, a reduction of 10 cases per 1000 and an increase of 42 cases per 1000]; low certainty)[34,35]. There was probably little difference between anti-VEGF monotherapy and anti-VEGF combined with PDT treatment in the incidence of systemic adverse events (*n* = 34; *RR*= 0.89 [95% *CI*, 0.06 to 13.08]; ARR, a decrease of 7 per 1000 population [95% *CI*, a reduction of 59 per 1000 population and an increase of 755 per 1000 population]; very low certainty)[34].

Compared with anti-VEGF combined with PDT treatment, anti-VEGF monotherapy may slightly reduce three BCVA letters per year in mean change from baseline (*n* = 542; MD= −3 [95% *CI*, −1.5 to −4.5]; low certainty)[30,32-35,37,38,40]. Subgroup analysis showed that patients treated with ranibizumab monotherapy had a slight reduction of four BCVA letters per year mean change from the baseline (MD= −4 [95% *CI*, −5 to −2.5]; high certainty)[30,32-34,37,40]; aflibercept monotherapy may not reduce patients' one-year BCVA letter mean change from baseline (MD= −0.5 [95% *CI*, −5 to −2.5]; moderate certainty)[35]; bevacizumab monotherapy may increase the one-year BCVA letter in mean change from baseline (MD= 5 [95% *CI*, −11 to 21]; low certainty)[38]. Anti-VEGF monotherapy may not reduce the edema regression rate in patients (RR= 0.98 [95% *CI*, 0.90 to 1.07]; ARR, a reduction of 18 cases per 1000 population [95% C*I*, a reduction of 88 cases per 1000 population and an increase of 61 cases per 1000 population]; moderate certainty)[35].

Compared with anti-VEGF combined with PDT treatment, the regression rate of polypoidal lesions in patients receiving anti-VEGF monotherapy was likely to be slightly reduced (RR= 0.62 [95% *CI*, 0.44 to 0.86]; ARR, a decrease of 223 cases per 1000 people [95% *CI*, a reduction of 328

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cases per 1000 population and a decrease of 82 cases per 1000 population]; low certainty) [30,34,36,37,39]. Subgroup analysis showed that ranibizumab monotherapy was likely to lead to a slight reduction in the regression of polypoidal lesions (RR= 0.54 [95%*CI*, 0.40 to 0.71]; ARR, a reduction of 304 cases per 1000 population [95% *CI*, a reduction of 396 cases per 1000 population and a reduction of 191 cases per 1000 population]; moderate certainty)[30,34,37,41]. However, there may be no difference in the regression rate of polypoidal lesions between the aflibercept combined with PDT treatment group and aflibercept monotherapy group (RR= 0.87 [95% *CI*, 0.65 to 1.16]; ARR, a decrease of 58 cases per 1000 [95% *CI*, a reduction of 157 cases per 1000 and a reduction of 72 cases per 1000]; moderate certainty)[36].

There was likely little difference in the one-year quality of life (measured by NEI-VFQ, Higher=Better); MD= −1.94 [95% *CI*, −3.94 to 0.05]; moderate certainty [35,42]) between the patients who received anti-VEGF monotherapy and anti-VEGF combined with PDT treatment. There may be little to no difference in the number of treatments between the two compared groups (MD= 0.42 [95% *CI*, −0.19 to 1.02]; low certainty)[32,34,35,40].

Certainty of the evidence of effects

The critical outcomes (the proportion of patients with BCVA gained or lost by 15 or more letters, the regression rate of polypoidal lesions observed on ICGA, and the number of treatments) were of low certainty of evidence. Therefore, the overall certainty of the evidence was low.

Other considerations

The ideal outcome of anti-VEGF combined with PDT treatment may be slightly better than that of anti-VEGF monotherapy. However, anti-VEGF monotherapy may result in moderate savings in medical costs. There was no significant uncertainty or difference in patients' values and preferences. The direct cost-benefit of anti-VEGF monotherapy and anti-VEGF combined with PDT treatment may depend on the economic model used and the duration of treatment. Furthermore, Anti-VEGF monotherapy may increase health equity and could be accepted and easily implemented by clinicians.

Panel discussion and conclusions

We suggest either anti-VEGF monotherapy or anti-VEGF combined with PDT treatment. The choice may depend on the patient's condition (such as the size or location of polypoidal lesions and the height of PED) or specific anti-VEGF agents.

Question 3 For PCV patients who plan to initiate anti-VEGF combined with PDT treatment, should PDT be combined initially (within one week after anti-VEGF injection) or later (after the loading phase of anti-VEGF)?

Recommendation 3 For PCV patients who plan to initiate anti-VEGF combined with PDT treatment, the guideline panel suggests later/rescue PDT over initial PDT (conditional recommendation, low certainty in the estimated effects).

Remarks: The timing of later/rescue PDT may be at least after three months of anti-VEGF according to treatment criteria of PDT (such as if polypoidal lesions were seen with subretinal fluid on the ICGA images obtained)[35,43].

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Summary of the evidence

Only one RCT study (n = 60)[43] was identified that addressed this question. The EtD framework is shown in **Supplementary Table 4**.

Benefits and harms

The initial PDT group may have a slight reduction of 2.64 in the number of additional treatments in one year (MD= −2.64 [95% *CI*, −3.68 to −1.6], low certainty[43]) compared with the later PDT group, excluding the immediate number of treatments (one PDT session with three anti-VEGF treatments for the initial PDT group; three anti-VEGF treatments for the later PDT group). Treatments with initial PDT may slightly increase the proportion of edema regression after treatment (RR= 1.12 [95% *CI*, 0.81 to 1.54]; ARR, 81 case reductions per 1,000 treated patients [95% *CI*, 129 case reductions per 1,000 treated patients and 336 case increases per 1,000 treated patients]; low certainty[43]). Treatments with initial PDT may slightly increase the proportion of regression of polypoidal lesions after treatment (RR= 1.13 [95% *CI*, 0.74 to 1.74]; ARR, 71 case reductions per 1,000 treated patients [95% *CI*, 143 case reductions per 1,000 treated patients and 406 case increases per 1,000 treated patients]; low certainty); and may increase the risk of subretinal hemorrhage (RR= 0.36 [95% *CI*, 0.02 to 8.39]; ARR, 21 case reductions per 1,000 treated patients [95% *CI*, 32 case reductions per 1,000 treated patients and 238 case increases per 1,000 treated patients]), but the evidence was very uncertain[43].

Treatments with initial PDT may result in little to no difference in the mean change in BCVA letters from baseline at one year when compared with later PDT treatment (MD=−0.7 [95% *CI*, −1.61 to 0.21]; low certainty[43]); Treatments with initial PDT may result in little to no difference in the proportion of patients with BCVA improvement of 15 letters or more (RR= 0.93 [95% *CI*, 0.54 to 1.60]; ARR, 34 case reductions per 1,000 treated patients [95% CI, 223 case reductions per 1,000 treated patients and 290 case increases per 1,000 treated]; low certainty[43]).

Certainty of the evidence of effects

All critical outcomes (mean change from baseline in the number of letters of BCVA, absence of edema on OCT, the proportion of participants who gained or lost 15 or more letters of BCVA, the regression rate of polypoidal lesions observed on ICGA, and the number of treatments) were of very low certainty of evidence. Therefore, the overall certainty of the evidence was low.

Other considerations

No significant uncertainties or variability were found in patients' values and preferences. Initial PDT treatment may be associated with moderate healthcare costs, may not be acceptable to patients, and is hard to implement.

Panel discussion and conclusions

We believe the benefits and harm were balanced when comparing initial versus later PDT with anti-VEGF treatment. We suggest clinicians consider the timing of therapy; PDT may benefit eyes that have failed anti-VEGF monotherapy by improving vision, eliminating fluid, and reducing the need for anti-VEGF retreatment. The PLANET study[35] (not included in this question because of ineligible comparison) reported the timing of later/rescue PDT, which could also be available as a reference.

Question 4 For PCV patients who plan to initiate anti-VEGF treatment, should the treatment regimen be pro re nata (PRN) or treat and extend (T&E) following three monthly loading doses?

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Recommendation 4 For PCV patients who plan to initiate the treatment with anti-VEGF, the guideline panel suggests T&E over the PRN regimen following three monthly loading doses

(conditional recommendation, very low certainty in the estimated effects).

Remarks: The T&E regimen increases the number of treatments compared to the PRN regimen, although it reduces the number of visits. The follow-up should consider the morphological changes of the fundus and pay more attention to the functional or conscious symptoms of the affected eye. The interval of T&E could be referred to in the ALTAIR study[44].

Summary of the evidence

No relevant studies in PCV patients were identified that addressed this question. Given that all the panelists suggest that most clinicians would use the same anti-VEGF strategy for nAMD to treat PCV, we take nAMD treatment plans to reference PCV. Only one RCT[45], including 77 AMD patients, compared the efficacy and safety between PRN and T&E regimens. Additional eight observational comparative studies[46-53] were identified. All PRN regimens included in the analysis had monthly monitoring following the loading phase. The EtD framework is shown in **Supplementary Table 5**.

Benefits and harms

Compared with the T&E regimen, the PRN regimen may reduce the incidence of a severe adverse event in AMD patients (*n* = 93; RR= 0.64 [95% *CI*, 0.16 to 2.52]; ARR, 38 case reductions per 1,000 treated patients [95% *CI*, 88 case reductions per 1,000 treated patients and 158 case increases per 1,000 treated patients]). Still, the certainty of the evidence was very low[45]. The PRN regimen could reduce the mean number of treatments in one year (*n* = 4,578; MD= −2.79 [95% *CI*, −3.37 to −2.21])[46-51], and the PRN regimen may increase the proportion of the patients with BCVA loss of 15 letters or more (*n* = 77; RR= 0.97 [95% *CI*, 0.26 to 3.62]; ARR, three case reductions per 1,000 treated patients [95% *CI*, 78 case reductions per 1,000 treated patients and 276 case increases per 1,000 treated patients]). Still, the certainty of the evidence was very low[45]. Compared with the T&E regimen, the PRN regimen reduced the mean changes in BCVA letters at one year from baseline in AMD patients (*n* =4,527; *MD* = −3.4 [95% *CI*, −5.53 to −1.28])[46,47,49-51]; may reduce the proportion of the patients with BCVA improvement of 15 letters or more by 33% (*n* = 77; RR=0.67 [95% *CI*, 0.33 to 1.39]; ARR, 113 case reductions per 1,000 treated patients [95% *CI*, 229 case reductions per 1,000 treated patients and 133 case increases per 1,000 treated patients])[45]; may reduce the risk of edema regression by 9% in AMD patients after treatment (*n* = 244; RR= 0.91 [95% *CI*, 0.54 to 1.54]; ARR, 55 case reductions per 1,000 treated patients [95% *CI*, 283 case reductions per 1,000 treated patients and 332 case increases per 1,000 treated patients]) [47,51]; may also increase the mean number of visits in one year by 2.08 (MD= 2.08 [95% *CI*, 0.63 to 3.52]), but the evidence was very uncertain.

Certainty of the evidence of effects

All critical outcomes (mean change from baseline in the number of letters of BCVA, absence of edema on OCT, the proportion of participants who gained or lost 15 or more letters of BCVA, and the number of treatments) were of very low certainty of evidence. Therefore, the overall certainty of the evidence was very low.

Other considerations

The PRN regimen may result in cost savings over the T&E regimen, though the difference in cost

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was insignificant. Likely, no significant uncertainties or variability were found in patient values and preferences.

Panel discussion and conclusions

We believe the benefits and harm were closely balanced when comparing PRN and T&E regimens following three monthly loading doses, whereas T&E regimen following three monthly loading doses was slightly better on treatment effect. Implementing the PRN regimen would burden patients and healthcare professionals due to monthly visits, thereby reducing its acceptability and feasibility.

Question 5 For PCV patients with persistent SRF or IRF on OCT after three monthly anti-VEGF treatments, should observation or continued anti-VEGF treatment be implemented?

Recommendation 5 For PCV patients with persistent SRF or IRF on OCT after three monthly anti-VEGF treatments, the guideline panel suggests continuing anti-VEGF treatment over observation (conditional recommendation, very low certainty in the estimated effects).

Remarks: Clinicians should closely observe changes in fundus morphology and function of the affected eye (or subjective symptoms) during follow-up and could consider stopping treatment when no clear benefit to visual acuity with further injection is expected, such as extensive subretinal scar formation.

Summary of the evidence

No RCTs or comparative observational studies were identified that addressed this question on target patients. Three non-comparative studies[54-56] were identified where the patient's developed tolerance to ranibizumab or bevacizumab and continued their treatment with aflibercept. Two other non-comparative studies[28,57] were recognized where adult patients with PCV and subretinal fluid never received any treatment. The EtD framework is shown in **Supplementary Table 6**.

Benefits and harms

Patients in the observation group did not receive treatment in the median of 84 (24–119) months of follow-up[28,57]. Only one study (n = 17) showed that, on average, patients in the anti-VEGF treatment continuation group received 8.8 times the treatment within one year (95% *CI*, 8.23 to 9.37; very low certainty)[56]. In terms of the mean change in the number of BCVA letters from baseline, patients in the observation group saw a mean BCVA loss of 15.52 letters after 24 – 119 months of follow-up (95% *CI*, –34.64 to 3.60; very low certainty)[28,57], whereas patients in the anti-VEGF treatment continuation group saw a BCVA increase of three letters after 6–12 months of follow-up (95% *CI*, 1 to 5.5; very low certainty)[54-56]. The proportion of patients with a BCVA increase of 15 letters or more in the observation group (after 24 – 56 months of follow-up) was 7% (95% *CI*, 0 to 34; very low certainty)[57], whereas the proportion in the anti-VEGF treatment continuation group (6 – 12 months of follow-up) was 25% (95% *CI*, 3 to 78; very low certainty)[54,56]. The proportion of patients with a BCVA loss of 15 letters or more in the observation group (24 – 119 months of follow-up) was 38% (95% *CI*, 13 to 72; very low certainty)[28,57], whereas the proportion in the anti-VEGF treatment continuation group (12 months of follow-up) was 18% (95% *CI*, 4 to 43; very low certainty)[56]. An incidence of regression of polypoidal lesions was 81%, which was only found in the anti-VEGF treatment continuation group (6 – 12 months of follow-up) (95% *CI*, 69 to 89; very low certainty)[54,56].

Certainty of the evidence of effects

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All critical outcomes (mean change from baseline in the number of letters of BCVA, the proportion of participants who gained or lost 15 or more letters of BCVA, the regression rate of polypoidal lesions observed on ICGA, the number of treatments, and absence of edema on OCT) were of very low certainty of evidence. Therefore, the overall certainty of the evidence was very low.

Other considerations

We considered that the harm associated with observation outweighed the benefits. There was no significant uncertainty or difference in patient values and preferences. In the case of subretinal fluid, drug withdrawal and observation could provide moderate cost savings. Drug withdrawal and observation may be easily accepted and implemented by key stakeholders.

Panel discussion and conclusions

We consider anti-VEGF treatment very efficacious and suggest continuing anti-VEGF treatment instead of discontinuing the treatment.

Question 6 For PCV patients with early massive subretinal hemorrhage (equal or more than four papillary diameters) involving the central macula, should treatment begin with surgery or anti-VEGF treatment?

Recommendation 6 For PCV patients with massive subretinal hemorrhage (equal or more than four papillary diameters) involving the central macula within the onset of 14 days, the panel suggests vitrectomy in combination with rtPA intraocular injection and Gas tamponade over anti-VEGF monotherapy (conditional recommendation, very low certainty in the estimated effects).

Remarks: Surgery may also benefit PCV patients with subretinal hemorrhage combined with vitreous hemorrhage; clinicians might consider using complementary therapy (e.g., pneumatic displacement, anti-VEGF, PDT, t-PA).

Summary of the evidence

No controlled studies were identified that addressed this question. Five observational studies[58-62] were identified evaluating PCV and nAMD patients with massive subretinal hemorrhage who underwent anti-VEGF or surgical treatment. Twenty-four non-comparative studies[46,63-84] evaluating PCV and nAMD patients who underwent anti-VEGF treatment and surgical treatment were also found (20 studies on surgical treatment, 4 studies on anti-VEGF treatment). The EtD framework is shown in **Supplementary Table 7**.

Benefits and harms

Compared with the surgical treatment group, the incidence of vitreous hemorrhage in the anti-VEGF treatment group within one year may be lower by 31% (n = 93; RR= 0.69 [95% CI, 0.27 to 1.74]; in terms of ARR, 62 cases or fewer per 1000 patients [95% CI, 146 cases or fewer per 1000 patients; 148 cases or more per 1000 patients]), but the certainty of the evidence was very low[60]. No other complications associated with anti-VEGF or surgical treatment were observed, including endophthalmitis, traumatic lens injury, or retinal detachment. Additionally, no systemic adverse events occurred in patients treated with anti-VEGF treatment[60].

Surgical treatment included pars plana vitrectomy (PPV), pneumatic displacement, PPV combined pneumatic displacement, t-PA combined with PPV, and pneumatic displacement.

In the 6 – 24 months of follow-up, compared with surgical treatment, anti-VEGF treatment may

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reduce the mean change in BCVA from baseline by nine letters (*n* = 305; *MD*= −9 [95% *CI*, −16.5 to −1]), but the certainty of the evidence was very low[58-61]. The proportion of patients with a BCVA increase of 15 letters or more may reduce (*n* = 141; *RR*= 0.61 [95% *CI*, 0.42 to 0.87]; ARR, 237 cases or fewer per 1000 patients [95% *CI*, 352 cases or fewer per 1000 patients; 79 cases or fewer per 1000 patients]), but the certainty of the evidence was very low[60,61].

In 1–72 months of follow-up, data from non-comparative studies showed that, on average, patients receiving anti-VEGF treatment improved their BCVA by 19.5 letters from baseline (95% *CI*, 13 to 26.5) (very low certainty), and patients receiving surgical treatment improved their BCVA by an average of 41.5 letters from baseline (95% *CI*, 31.5 to 51.5) (very low certainty)[42,63-85]. The proportion of patients receiving anti-VEGF treatment with a BCVA increase of 15 letters or more was 51% (95% *CI*, 39% to 63%) (very low certainty), and the proportion of patients receiving surgical treatment with a BCVA increase of 15 letters or more was 71% (95% *CI*, 60% to 81%) (very low certainty)[42,63,64,66-72,78]. In patients receiving anti-VEGF treatment, the proportion of those with a BCVA loss of 15 letters or more was 20% (95% *CI*, 12% to 30%) (very low certainty). Among patients receiving surgical treatment, the proportion of those with a BCVA loss of 15 letters or more was 11% (95% *CI*, 7% to 16%) (very low certainty)[42,63,64,67,68,70,72]. The results of a subgroup analysis (patients with subretinal hemorrhage, patients with vitreous hemorrhage, and different surgical methods) reached similar conclusions.

In the one-year follow-up, data from non-comparative studies also showed that, in patients receiving anti-VEGF treatment, the regression rate of polypoidal lesions was 22% (95% *CI*, 9% to 42%), and the average number of received treatments was 4.21 (95% *CI*, 2.92 to 5.49)[63,67].

Certainty of the evidence of effects

All critical outcomes (mean change from baseline in the number of letters of BCVA, the proportion of participants who lost 15 or more letters of BCVA, the regression rate of polypoidal lesions observed on ICGA, and the number of treatments) were of very low certainty of evidence. Therefore, the overall certainty of the evidence was very low.

Other considerations

Compared with anti-VEGF treatment, surgical treatment is associated with the significant benefit of vision improvement, significantly outweighing the harm. There was no considerable uncertainty or difference in patient values and preferences. Anti-VEGF treatment costs almost as much as surgical treatment, which is acceptable and feasible among patients and clinicians.

Panel discussion and conclusions

When compared to the improved efficacy associated with surgical treatment, the panel suggests surgery (*e.g.*, anti-VEGF, PDT, tissue-Plasminogen Activator [t-PA], pneumatic displacement) over anti-VEGF treatment only for PCV patients with massive subretinal hemorrhage (equal or more than four papillary diameters) involving the central macula. The proposed surgery timing for surgery would be within two weeks of the occurrence of subretinal hemorrhage.

DISCUSSION

When compared to previous guidelines or consensus reports on PCV treatment[7,10,11], we produced the first evidence-based guidelines adhering to the Institution of Medicine standard, providing six common scenarios (clinical practice question-based) for the management of PCV, incorporating the

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best available evidence on the benefits and harms of the interventions, patients values and preference, resources usage, feasibility, accessibility, transparently reporting panel's considerations, and judgments for the decision-making process. This guideline proposed several consistent recommendations (such as the optimal treatments for treatment-naïve patients, the optimal regimens when using anti-VEGF monotherapy, or combined with PDT treatment) with previous guidelines or consensus[7,10,11] based on more comprehensive evidence. Furthermore, this guideline addresses common yet unanswered clinical questions such as the continuation of anti-VEGF drugs and the treatment options for massive subretinal hemorrhage. Our clinical questions were designed to follow the PCV treatment process and provide a holistic approach covering most situations encountered in clinical practice (**Figure 2**).

The panel made six conditional recommendations requiring shared-decision between clinicians and individual patients based on the specific disease manifestations and patients' preferences.

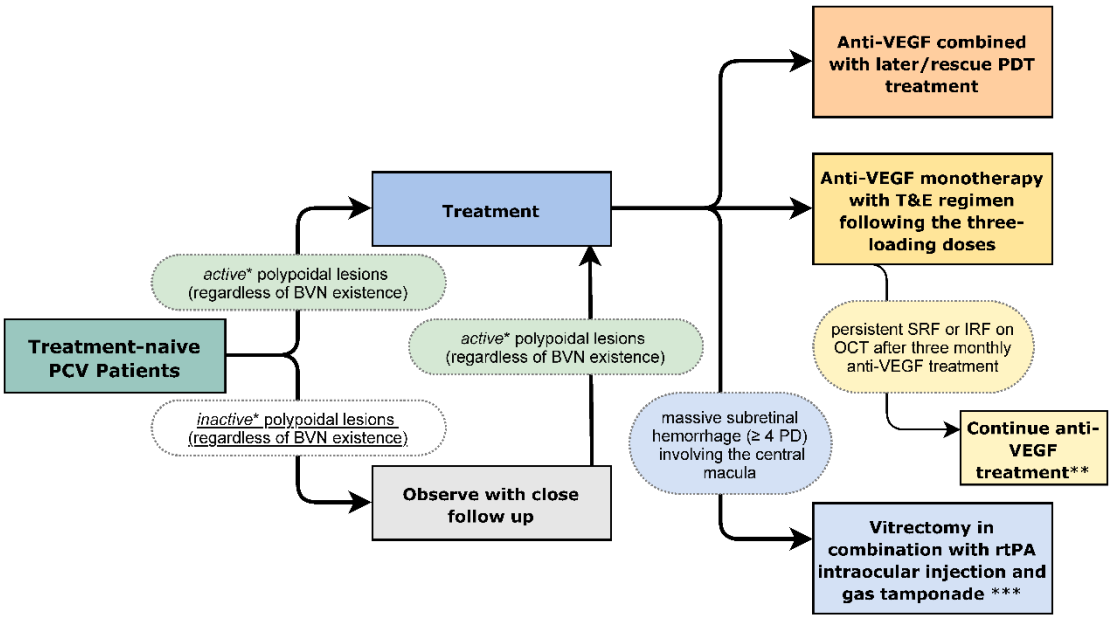

Figure 2 Recommendations for clinical questions (listed in Figure 1) on clinical management of PCV.

Notes: VEGF: vascular endothelial growth factor; BVN: branching vascular network; PCV: polypoidal choroidal vasculopathy; PD: pneumatic displacement; PDT: photodynamic therapy; OCT: optical coherence tomography; SRF: subretinal fluid; T&E: treated and extend.
*active: subretinal fluid, intraretinal fluid or subretinal hemorrhage or vitreous hemorrhage on OCT or fundoscopy; inactive: without subretinal fluid, intraretinal fluid or subretinal hemorrhage or vitreous hemorrhage on OCT or fundoscopy
**Clinicians should closely observe the change in fundus morphology and function of the affected eye (or subjective symptoms) during follow-up, and could consider to stop treatment in cases when no clear benefit to visual acuity with further injection is expected, such as large subretinal scar formation.
***For patients with PCV and subretinal hemorrhage combined with vitreous hemorrhage, the recommendations apply as well.

Some of the questions in our guideline only had low and very low certainty evidence to support the recommendations. Since PCV is mostly prevalent in Asian patients, only a few high-quality RCTs were conducted compared to PDT and anti-VEGF therapy. Studies[41,86-90] which investigated another commonly used anti-VEGF in China, conbercept, were not included in the body of evidence. Two

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studies do not address the guideline questions. Huang *et al.*[41] reported a retrospective case-control study comparing the short-term efficacy of conbercept and ranibizumab. Cheng *et al.*[86] aimed to compare the outcomes of conbercept therapy between two different angiographic subtypes of PCV. The other four studies were not included due to levels of evidence. A retrospective comparative study (Li *et al.*[90]) compared the short-term efficacy of conbercept monotherapy and conbercept combined with PDT treatment. No clear differences were identified between the two compared groups. Ye *et al.*[87] and Peng *et al.*[89] reported non-comparative studies which evaluated the functional and structural outcomes of conbercept monotherapy using a PRN regimen following three monthly loading doses. Qi *et al.*[88] reported a non-comparative study evaluating the real-life clinical outcomes of conbercept combined rescue therapy for PCV patients. The guideline panel was concerned that the AURORA study[4] of conbercept on nAMD (including PCV) was designed with a three-loading regimen to initiate anti-VEGF (believed to be the consensus of the Chinese PCV experts who drafted the clinical trial at that time). Therefore, when starting treatment with conbercept, the guideline panel recommended starting with three injections of conbercept once a month according to the regimen reported in the AURORA study. Regarding salvage therapy, the guideline panel also suggests that salvage therapy with PDT is effective for patients with poor outcome after three loading injections of conbercept, which can be used as a reference for clinical practice. Firm conclusions on conbercept need more comparative studies.

We identified several research gaps during guideline development, such as the lack of RCTs evaluating surgery in patients with massive subretinal hemorrhage and treatment options for patients with special conditions like inactive PCV. Questions remain to be answered in the future regarding the management of PCV. For instance, information is needed regarding the effect of upcoming sustained-release anti-VEGF drugs, other treatment modalities—especially for those challenging cases—different methods of PDT, injection regimens other than T&E or PRN, the timing of surgery, and the procedures available for breakthrough vitreous hemorrhages. Future high-quality RCTs are needed to compare the effectiveness and safety of different anti-VEGF agents.

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Author contributions

You-xin Chen and Yu-qing Zhang provide conceptualization; You-xin Chen, Yu-qing Zhang, Wei-hong Yu, and Fang Qi drafted and revised the manuscript; Chang-zheng Chen, Hong Dai, Su-yan Li, Xiang Ma, Xiao-dong Sun, Shi-bo Tang, Yu-sheng Wang, Wen-bin Wei, Feng Wen, Ge-zhi Xu, Mei-xia Zhang, Ming-wei Zhao, Xiao-xin Li, and Xun Xu reviewed the manuscript and provided suggestions for improvement; members of evidence synthesis team, Yang Zhang and Fang Qi, contributed evidence summaries to the guidelines. All authors approved the final version of the guideline.

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Conflict of interest disclosure

You-xin Chen and Wei-hong Yu served on academic lectures for Bayer, Novartis, and KangHong pharmaceutical. Xiang Ma received research support from KangHong pharmaceutical for an investigator-initiated clinical trial on effectiveness of conbercept in patients with high myopia with macular degeneration (Achieve in 2019.12.31). Feng Wen received research support from KangHong pharmaceutical for a prospective clinical controlled trial of the efficacy of intravitreal injection of conbercept in patients with PCV (with RPE breakthrough versus without RPE breakthrough in polyp foci) and support from Novartis for a randomized, double-blinded, multicenter trial on efficacy and safety of Brolucizumab (6mg) versus aflibercept in Chinese patients with nAMD. All the other authors reported no relevant commercial relationships.

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