Predictive factors of resolved retinal fluid after intravitreal ranibizumab for polypoidal choroidal vasculopathy

Hideki Koizumi, Tetsuya Yamagishi, Taizo Yamazaki, Shigeru Kinoshita

ABSTRACT

Background/aims To investigate the predictive factors for the resolution of retinal fluid after intravitreal injections of ranibizumab (IVRs) for polypoidal choroidal vasculopathy (PCV).

Methods Forty-seven eyes of 45 patients with symptomatic PCV received 0.5 mg of IVR monthly for 3 months. One month after the third IVR, the presence of dry macula, defined as absence of retinal fluid as detected by the use of optical coherence tomography, was retrospectively evaluated and correlated with clinical characteristics at baseline. Most of the eyes were followed for over 6 months.

Results Of the 47 eyes, 31 eyes (66%) achieved the dry macula along with increased best-corrected visual acuity (BCVA) (0.64 to 0.46 logarithm of the minimum angle of resolution units, p<0.0001), while the other 16 eyes without dry macula showed no significant change of BCVA. Univariate analyses of the baseline characteristics identified the smaller size of the largest polyp (p=0.0008) and the absence of serous or haemorrhagic pigment epithelial detachment (p=0.045) as predictive factors for the dry macula. Multivariate logistic regression found the independent predictor for the dry macula to be the smaller size of the largest polyp (p=0.001). No severe systemic or ocular adverse events were observed.

Conclusions IVR may be helpful for resolution of retinal fluid and increased BCVA in the short term, but larger polyps and pigment epithelial detachments at baseline may be negative prognostic factors for a therapeutic response. Further studies are needed to clarify the long-term efficacy of IVR for PCV.

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is considered to be one of the subtypes of exudative age-related macular degeneration and is characterised by abnormal branching vascular networks with polypoidal lesions located in the inner choroid.1–3 Uyama and associates4 reported the natural progression of PCV eyes, in that 50% of the patients in that study had a favourable course whereas the other half had repeated bleeding and leakage, resulting in macular degeneration and visual loss. Many previous studies have proven the efficacy of photodynamic therapy (PDT) with verteporfin for PCV, with resolution of polyps and associated fluid which led to improvement or stabilisation of visual outcome.5–15 However, one of the main concerns with PDT is subretinal or subpigment epithelial haemorrhage.7 12 13 16 In addition, long-term follow-up has shown that the improved or stabilised visual outcome might not be maintained should there be a recurrence of disease activity.17–19 Therefore, it is important to seek alternative methods for the treatment of PCV.

Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents, specifically, bevacizumab and ranibizumab (Lucentis; Genentech, South San Francisco, California, USA), reportedly demonstrated reduction of exudation from PCV with various visual outcomes.20–25 However, such agents were not effective for diminishing the abnormal choroidal vasculature itself. Thus, the potential efficacy of anti-VEGF treatment for PCV is still difficult to assess.

It should be noted that there is some rationale for using anti-VEGF treatment for PCV. First, it is known that VEGF is upregulated in the aqueous humour in eyes with PCV.26 Second, specimens obtained from the eyes with PCV also showed strong expression of VEGF in vascular endothelial cells and retinal pigment epithelium cells.27 On the other hand, another histopathologic study was unable to identify VEGF in vascular endothelial cells in PCV specimens, although VEGF was still found in the retinal pigment epithelium cells.28 Therefore, the contribution of VEGF in the pathogenesis of PCV seems to vary among cases. If the clinical characteristics related to the response to anti-VEGF agents before starting treatment of PCV can be fully elucidated, then that might prove helpful for choosing proper treatment strategies.

The purpose of this study was to find the predictive clinical factors for the resolution of retinal fluid from PCV after intravitreal injections of ranibizumab (IVRs) in the short term. We believe that this current study provides additional information for the management of PCV.

MATERIALS AND METHODS

This study included 47 eyes of 45 consecutive cases (35 eyes of 34 males and 12 eyes of 11 females) with symptomatic PCV involving the subfoveal region. The major exclusion criteria were past treatment histories of PCV, previous vitrectomy, cataract surgery within the past 90 days, a history of systemic vascular events such as myocardial infarction or cerebral vascular accidents, and uncontrolled hypertension. All eyes had at least one of the following at baseline: (1) subretinal fluid, (2) intraretinal fluid or (3) subretinal haemorrhages, all of which could be detected by a spectral-domain optical coherence tomography (OCT) (3D OCT1000; TOPCON Corp, Tokyo, Japan).

At baseline, all eyes had complete ophthalmic
examinations including best-corrected visual acuity (BCVA) testing with Landolt C charts, colour fundus photography, and fluorescein angiography (FA) and indocyanine green angiography (ICGA) using a confocal scanning laser ophthalmoscopy (HRA-2; Heidelberg Engineering Inc, Dossenheim, Germany). The diagnosis of PCV was confirmed with characteristic polypoidal vascular lesions and branching choroidal vascular networks revealed by ICGA. Sometimes, PCV lesions could be detected funduscopically by the presence of an orange—red retinal protrusion over the polyps.

All patients received 0.5 mg of IVR monthly for 3 months; at baseline, at 1 month and at 2 months. At 3 months, the frequency of ‘dry macula’, which was defined as absence of subretinal or intraretinal spaces detected by use of OCT, was investigated. All cases, except for two cases experiencing nausea at the baseline angiography, underwent FA and ICGA at 3 months for follow-up, and the morphologic changes on ICGA were also examined. From that point onward, the patients received additional IVRs according to the discretion of the physicians, or when the patients wished, PDT with verteporin was administrated as an alternative treatment. Most of the eyes were followed over 6 months. In addition to the biomicroscopic examination, BCVA testing and OCT were performed monthly at every visit.

As for the possible factors that might influence the achievement of dry macula, we considered several factors at baseline. The data consisted of age, gender, BCVA at baseline, the size of choroidal vascular networks on ICGA, the size of the largest polyp, presence of serous or haemorrhagic pigment epithelial detachment (PED), presence of lipid deposition, presence of fluid accumulation or haemorrhage involving the fovea on OCT images at baseline. BCVA at baseline ranged from −0.08 to 1.70 logMAR units (mean: 0.68; median: 0.70).

At 3 months, 31 of the 47 eyes (66%) achieved the dry macula. The mean BCVA of the 47 eyes improved from baseline to 3 months (0.68 to 0.57 logMAR units, p = 0.0046). Of the 47 eyes, 11 eyes (24%) showed increased BCVA of 0.3 or more logMAR units. Among the 35 eyes (76%) that maintained baseline BCVA and three eyes (6%) that showed decreased BCVA of 0.3 or more logMAR units. Although BCVA at baseline was not significantly different, the eyes with dry macula showed significantly better BCVA with improvement than those without dry macula (figure 1). The eyes without the dry macula did not show significant change of BCVA after treatments.

The results of the univariate analyses are shown in the table 1. The results of the analyses showed that the factors associated with dry macula were the smaller size of the largest polyp (p = 0.0008) and the absence of PED (p = 0.045). Forward stepwise logistic regression of factors revealed that the smaller size of the largest polyp was the sole factor associated with the dry macula (p = 0.001). At baseline, nine eyes had serous or haemorrhagic PED. Of those nine eyes, PED decreased in four eyes and remained stable in five eyes. A new PED developed in one of the 38 eyes without PED at baseline.

FA and ICGA were able to be performed and evaluated at 3 months in 45 of the 47 eyes. Of those 47 eyes, nine eyes (19%) exhibited complete resolution of polyps, 12 eyes (26%) showed partial regression of polyps and one eye (2%) demonstrated an increased number of polyps compared to the baseline. In the remaining 25 eyes (56%), the polyps were unchanged. Of the nine eyes with complete resolution of polyps, all eyes but one achieved the dry macula. No eyes revealed significant regression of the branching vascular networks.

Twenty-six of 31 eyes with dry macula at 3 months were able to be followed up monthly over a 6-month period. Of those 26 eyes, a mild recurrence of subretinal or intraretinal fluid was seen in 13 eyes (50%); in 10 eyes at 4 months, in one eye at 5 months, and in the other two eyes at 6 months. Of those 15 eyes, additional IVRs were given to 12 eyes according to the discretion of
Table 1  Univariate analyses of baseline characteristics associated with dry macula after 3 monthly injections of intravitreal ranibizumab

<table>
<thead>
<tr>
<th>Clinical characteristics at baseline</th>
<th>Dry macula (+)</th>
<th>Dry macula (−)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) ± SD</td>
<td>73.4±7.3</td>
<td>77.5±7.5</td>
<td>0.10</td>
</tr>
<tr>
<td>Female (%)</td>
<td>9 (29)</td>
<td>3 (19)</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean logMAR BCVA ± SD</td>
<td>0.64±0.36</td>
<td>0.75±0.42</td>
<td>0.43</td>
</tr>
<tr>
<td>Mean size of the vascular networks (μm) ± SD</td>
<td>3412±1396</td>
<td>3549±887</td>
<td>0.47</td>
</tr>
<tr>
<td>Mean size of the largest polyp (μm) ± SD</td>
<td>320±128</td>
<td>597±291</td>
<td>0.0008**</td>
</tr>
<tr>
<td>Mean number of polyps</td>
<td>3.1</td>
<td>3.9</td>
<td>0.78</td>
</tr>
<tr>
<td>Concurrent type-2 CNV (%)</td>
<td>4 (13)</td>
<td>1 (6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Choroidal vascular hyperpermeability (%)</td>
<td>3 (10)</td>
<td>4 (25)</td>
<td>0.21</td>
</tr>
<tr>
<td>Subretinal fluid (%)</td>
<td>27 (87)</td>
<td>15 (94)</td>
<td>0.65</td>
</tr>
<tr>
<td>Intraretinal fluid (%)</td>
<td>15 (48)</td>
<td>5 (31)</td>
<td>0.35</td>
</tr>
<tr>
<td>Lipid deposition (%)</td>
<td>13 (46)</td>
<td>7 (44)</td>
<td>0.91</td>
</tr>
<tr>
<td>Subretinal haemorrhage (%)</td>
<td>3 (10)</td>
<td>5 (31)</td>
<td>0.10</td>
</tr>
<tr>
<td>Pigment epithelial detachment (%)</td>
<td>3 (10)</td>
<td>6 (38)</td>
<td>0.045*</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01.

BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; logMAR, logarithm of the minimal angle of resolution.

the physicians, while PDT was applied on the other one eye at the request of the patient. The remaining 15 eyes (50%) showed no recurrence over 6 months without additional IVRs.

Fifteen of the 16 eyes without dry macula at 3 months were able to be followed up monthly over a 6-month period. Of those 15 eyes, 11 eyes received additional IVRs according to the discretion of the physicians throughout the 6 months, but only one eye achieved temporary resolution of fluid during that period. Of the other four eyes, three eyes underwent PDT and one eye received PDT combined with IVR, at the request of the patients.

During the 6-month observation period, one eye treated with IVR alone developed two disc areas of subretinal haemorrhage at 5 months, but BCVA was not affected. No other systemic or ocular adverse events were observed during that 6-month period. Representative examples from the above-described cases are shown in figures 2 and 3.

**DISCUSSION**

This study demonstrated that the size of the largest polyp on ICGA and the presence of PED might be a possible factor that predicts the persistent retinal fluid from PCV after monthly IVRs for 3 months by the univariate analyses. Multivariate logistic regression found the independent predictor for the persistent retinal fluid in the macula to be the size of the largest polyp. Previous reports consistently demonstrated that intravitreal injections of bevacizumab or IVRs reduced the fluid from PCV, but did not diminish the abnormal choroidal vasculature itself.20–25 No previous reports have shown the factors predicting the changes of retinal fluid after IVRs for PCV. The persistent retinal fluid at 3 months rarely resolved in spite of additional IVRs through 6 months, whereas half of the PCV eyes without fluid at 3 months, and that received no additional treatment through the 6-month period, showed no recurrence. Thus, this information may be helpful when physicians consider the optimal treatment for PCV.

Maintaining a normal retinal anatomy without pathologic fluid accumulation is reportedly important for the management of exudative age-related macular degeneration with IVR.29 30 In this present study, the eyes with dry macula at 3 months showed increased BCVA, while those without dry macula exhibited no significant change in BCVA. Thus, for the treatment of PCV with large polyps and/or PEDs, IVR may actually be less frequently helpful for improving the retinal anatomy and the visual outcome.

Resolution of the polypoidal lesions appears to be directly related to the resolved fluid, as shown by the previous reports using thermal photocoagulation31 and PDT.5–15 Our study also demonstrated that eight of the nine eyes that achieved complete

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**Figure 2** The right eye of a 76-year-old man with polypoidal choroidal vasculopathy. Indocyanine green angiography at baseline (A) showed small polypoidal lesions (arrows) and abnormal branching vascular networks. The size of the largest polyp was 380 μm. Vertical optical coherence tomography (C) showed subretinal fluid accumulation in the macula. One month after 3 monthly intravitreal injections of ranibizumab, indocyanine green angiography demonstrated complete resolution of polyps (B). No fluid was detected with optical coherence tomography (D).
resolution of polyps also exhibited a dry macula. Thus, monitoring the morphologic changes on ICGA may also be valuable in the management of PCV with IVR. The rates of complete resolution or decreased number of polyps after one to three intravitreal injections of bevacizumab or IVRs have reportedly ranged from 9% to 80%.20

However, the rate was 45% (complete resolution of polyps in 19% and decreased number of polyps in 26%) in the current study. The reason behind these different resolution rates might be explained by the fact that PCV lesions vary histopathologically among cases.27 28 32 In the discussion in a previous report regarding bevacizumab treatment for PCV, Gomi and associates anticipated that ranibizumab might penetrate more deeply into the choroidal vascular abnormalities and might provide better efficacy for the treatment of PCV, thanks to its smaller molecular weight and higher affinity for VEGF than that of bevacizumab.21 Our study showed only a moderate effect on diminishing the polyps, similar to the result of 33% that Kokame and associates23 reported with IVRs. Moreover, the findings of this present study showed that the branching vascular network vessels did not show significant regression after IVRs, as was reported before.21 25 Previous studies have reported that persistence of the branching vascular networks was also observed in most of the eyes treated with PDT and that the persistence was presumably associated with the recurrence of polyps and resultant exudative changes.18 19 35 Therefore, future treatment strategies for PCV should include a careful observation of the polyps and the branching vascular networks.

In this present study, we were unable to draw a definitive conclusion as to why PCV with large polyps had a poorer response to IVRs. One possibility is that a 0.5 mg monthly administration of IVRs is an insufficient dosage to suppress vascular hyperpermeability of the large polyps. Song and associates24 reported the results of administering a single intravitreal injection of 1.25 mg or 2.5 mg bevacizumab in 19 PCV eyes. Although the dose selection in that study was not randomised, they found that there was no significant difference in the changes in central retinal thickness at 3 months between the two doses. At least in the case of bevacizumab, there seemed to be no dramatic response yielded by the escalated dose. Another possible reason might be attributed to the hypothesis that PCV with large polyps may develop with less contribution of VEGF than PCV with small polyps. However, the precise role of VEGF in the pathogenesis of PCV is a question that remains to be investigated.

In this present study, though not strong, the presence of PED at baseline was also statistically significant in univariate analyses for the persistent retinal fluid. Saito and associates14 applied PDT on eyes with PCV with serous PED and noted anatomic improvement and gain in BCVA at 12 months, and those results were similar to the outcome of eyes without PED. For eyes with PED, further studies are needed to evaluate the long-term benefits and risks of each treatment.

This study has limitations inherent to the retrospective nature and the short follow-up period. In addition, although relatively large compared to the previous reports, the number of patients was too small to draw definite conclusions. Furthermore, the variable treatment decisions after the first 3 months of IVR treatment might be a weaker part of the study design. However, we demonstrated that the size of the largest polyps and the presence of PED might influence the resolution of fluid from PCV. In other words, we found that there is a certain subgroup of PCV eyes showing favourable responses to IVR in the short term. Further studies with longer follow-up are needed to clarify the long-term efficacy of IVR for PCV.
Competing interests None.

Ethics approval Ethics approval was provided by the Institute Review Board of Kyoto Prefectural University of Medicine.

Contributors Involved in design and conduct of study (HK); data collection (HK, TY, TS); analysis and interpretation of the data (HK); and writing (HK), critical revision (TY, SK) and approval (HK, TY, SK) of the manuscript.

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