1    **One-year outcomes of a treat-and-extend regimen of intravitreal aflibercept for**

2    **polypoidal choroidal vasculopathy**

3

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14   **Running title:**

15   Treat-and-extend regimen for PCV

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24  **Abstract**

25  *Purpose*  To evaluate the 1-year treatment outcomes of intravitreal aflibercept injections

26  (IVA) using a treat-and-extend regimen for polypoidal choroidal vasculopathy (PCV).

27  *Methods*  Thirty-seven eyes with treatment-naive PCV treated with IVA using a treat-and-extend

28  regimen for 1 year were reviewed retrospectively. The main outcome measures were changes in

29  the best-corrected visual acuity (BCVA) and central retinal thickness (CRT), and the treatment

30  interval at 1 year. The predictive factors for patients who could not continue to extend the

31  treatment interval because of poor response to IVA or recurrence were analyzed.

32  *Results*  The mean logarithm of the minimum angle of resolution BCVA improved from

33  0.37 at baseline to 0.21 at 1 year ($P < 0.001$). The mean CRT decreased from 342.3 μm at

34  baseline to 196.6 μm at 1 year ($P < 0.001$). The mean treatment interval was 9.7 weeks at

35  1 year (4 weeks in 11 eyes [29.7%], 6 weeks in 1 eye [2.7%], 8 weeks in 2 eyes [5.4%], 10

36  weeks in 1 eye [2.7%], and 12 weeks in 22 eyes [59.5%]). A larger number of polypoidal

37  lesions at baseline was predictive for patients who could not continue to extend the

38  treatment interval.

39  *Conclusions*  IVA using a treat-and-extend regimen is effective for improving BCVA and

40  CRT in eyes with PCV.

41

42  **Keywords** Aflibercept, Polypoidal choroidal vasculopathy, Treat-and-extend regimen

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## Introduction

46 Polypoidal choroidal vasculopathy (PCV) is an exudative maculopathy affecting vision,

47 with a prevalence of 10% to 54% in Asian patients and 8% to 12% in white patients with

48 presumed exudative age-related macular degeneration (AMD) [1, 2]. Clinically, PCV,

49 which is characterized by polypoidal lesions and a branching vascular network seen on

50 indocyanine green angiography (ICGA) [3, 4], causes recurrent retinal hemorrhages, fluid

51 accumulation, and lipid exudation, eventually resulting in chorioretinal atrophy and

52 permanent visual loss [5].

53       The therapeutic approaches to PCV include photodynamic therapy (PDT),

54 intravitreal injections of antivascular endothelial growth factor (VEGF) pharmacologic

55 agents, and a combination of both. Although previous studies have reported that PDT is

56 more effective than anti-VEGF drugs, such as ranibizumab, for causing regression of the

57 polypoidal lesions, the visual outcomes were reportedly better in patients who received

58 anti-VEGF therapy than in those who received PDT [2, 6]. The limited visual

59 improvement with PDT might result from subretinal hemorrhages, pigment epithelial

60 tears, or atrophy of both the retinal pigment epithelium and the choriocapillaris in the area

61 to which PDT is applied [7–9]. Therefore, because of their efficacy and safety, anti-VEGF

62 drugs are considered an important therapeutic option. Of the various anti-VEGF drugs

63 available, aflibercept (Eylea; Regeneron, Tarrytown, USA) reportedly has a higher

64 binding affinity to VEGF, a longer intravitreal half-life relative to other anti-VEGF agents,

65 and the capacity to antagonize growth factors other than VEGF [10–13]. Recently, we

66 reported the efficacy of intravitreal aflibercept injections (IVA) for improving visual

67 acuity (VA) and causing regression of polyps in eyes with PCV [14].

68    Regarding the treatment regimens of anti-VEGF therapy, treat-and-extend regimens

69    have recently been used to treat AMD [15, 16]. A treat-and-extend regimen is an

70    individualized regimen that aims to decrease the numbers of clinic visits and injections by

71    determining the optimal treatment interval [17]. Specifically, the interval between

72    injections is extended gradually after resolution of the retinal exudation in response to

73    initial monthly injections. With recurrence, the interval is shortened. The efficacy of a

74    treat-and-extend regimen in controlling disease activity and improving VA with fewer

75    clinical visits and injections as compared with other regimens, such as fixed dosing and

76    pro re nata (PRN) regimens, has been reported in patients with AMD [18–23]. However,

77    to the best of our knowledge, no reports have evaluated a treat-and-extend regimen for

78    treating PCV.

79    In the current study, we evaluated the 1-year outcomes of a treat-and-extend regimen

80    with IVA used to treat previously untreated PCV to clarify the effectiveness of this

81    approach. We also sought to identify the prognostic factors for patients who could not

82    continue to extend the treatment intervals because of poor response to IVA or recurrence

83    of PCV.

84

85    **Patients and methods**

86    We retrospectively reviewed the medical records of 37 eyes of 37 consecutive

87    patients with treatment-naive PCV who had been treated with IVA using a treat-and-

88    extend regimen for at least 1 year at Okayama University Graduate School of Medicine,

89    Dentistry and Pharmaceutical Sciences between June 2013 and August 2014. The

90    institutional review board of this institution approved the study, which was conducted

91  according to the tenets of the Declaration of Helsinki. PCV was diagnosed on the basis of

92  the presence of abnormal branching vascular networks and characteristic polypoidal

93  vascular lesions seen on ICGA images. Eyes with other retinal diseases, ie, diabetic

94  retinopathy, retinal vein occlusion, or myopic degeneration, were excluded from the study,

95  as were eyes that had undergone vitrectomy.

96  All the patients underwent a comprehensive ophthalmologic examination at all

97  visits, which included measurement of decimal best-corrected VA (BCVA) using a

98  Landolt C acuity chart at 5 meters and intraocular pressure, indirect ophthalmoscopy, slit-

99  lamp biomicroscopy with a contact lens, and optical coherence tomography (OCT)

100  (swept-source OCT, DRI OCT-1 Atlantis; Topcon, Tokyo, Japan, or spectral-domain

101  OCT, Spectralis; Heidelberg Engineering, Heidelberg, Germany). Fluorescein

102  angiography (FA) and ICGA were performed at baseline and at 3 months and 1 year (12

103  months up to 15 months) after the primary aflibercept injection. FA and ICGA images

104  were obtained using the Heidelberg Retina Angiograph system (Heidelberg Engineering,

105  Dossenheim, Germany) with a confocal scanning laser ophthalmoscope. The

106  greatest linear dimension (GLD) of the lesions was measured by both FA and ICGA. The

107  GLD on FA includes areas of dye leakage, pigment epithelial detachments, and subretinal

108  hemorrhages. The GLD on ICGA includes areas of polypoidal lesions and abnormal

109  branching vascular networks.

110  All the patients were initially treated with at least 3 monthly IVA (2 mg). The

111  monthly injections continued until no retinal exudation (ie, new subretinal hemorrhages or

112  subretinal and/or intraretinal fluid) was observed on OCT or slit-lamp biomicroscopy.

113  When the retinal exudation resolved, the interval to the next injection and follow-up

114    period was extended by 2 weeks up to a maximum of 12 weeks, at which point the

115    treatment was maintained at that interval. If the exudation recurred, the interval was

116    shortened by 2 weeks to a minimum interval of 4 weeks. When the retinal exudation

117    resolved after a reduced interval, the treatment was maintained at this frequency. Interval

118    extensions were restarted if no recurrence was observed for 6 consecutive months.

119         The BCVA was converted to logarithm of the minimum angle of resolution

120    (logMAR) units for statistical analysis. After the BCVA had been assessed, the eyes were

121    categorized into the following 3 groups on the basis of the BCVA change at 1 year from

122    baseline (change defined as $\geq 0.3$ logMAR units): improved, stable, and deteriorated.

123    Complete resolution of the polypoidal lesions was evaluated by ICGA at 3 months and at 1

124    year after the first injection. The number of injections and visits during the first year and

125    the intervals between the injections at 1 year were also calculated. The changes in the

126    BCVA and central retinal thickness (CRT) between baseline and 1 year after the first

127    injection were compared using the paired *t* test. We used the Mann-Whitney test to

128    compare the changes in the BCVA and CRT between eyes with no recurrence and eyes

129    with poor response or recurrence. Poor response to IVA was defined as persistent retinal

130    exudative changes, including subretinal hemorrhages and fluid accumulation, for 1 year

131    despite IVA every 4 weeks. To identify the prognostic factors for patients who could not

132    continue to extend treatment intervals because of poor response to IVA or recurrence of

133    PCV, multivariate logistic regression analysis was performed. The factors included in this

134    analysis were patient age, BCVA, CRT, GLD on FA, GLD on ICGA, the number of polyps

135    and size of the largest polyp at baseline, and regression of the polypoidal lesions at 3

136    months after the first IVA. We calculated the odds ratios (ORs) and 95% confidence

137    intervals (CIs) for poor response or recurrence of PCV. All statistical analyses were

138    performed with version 22.0 SPSS software (IBM, Armonk, USA). Probability values less

139    than 0.05 were considered significant.

140

141                                                **Results**

142        The mean patient age was 73.3 years (range, 55–89). Seven of the 37 patients were

143    female. All 37 eyes had retinal exudative changes, including subretinal hemorrhages and

144    fluid accumulation involving the fovea, on the baseline OCT images. During the follow-

145    up period, no adverse events occurred and all the patients could follow the protocol.

146        At baseline, the mean GLD on FA was 3629.1 μm (range, 1459–9482); the mean

147    GLD on ICGA was 2427.3 μm (range, 1252–6358); the mean number of polyps was 2.9

148    (range, 1–8); and the mean diameter of the largest polyp was 275.8 μm (range, 122–581).

149    The polypoidal vascular lesions or abnormal branching vascular networks were at the

150    subfovea in all eyes.

151        The mean logMAR BCVA of the 37 eyes improved significantly from $0.37 \pm 0.37$

152    (range, -0.18 to 1.52) at baseline to $0.21 \pm 0.29$ (range, -0.18 to 1.10) at 1 year ($P < 0.001$)

153    (Fig. 1a). The BCVA improved in 11 eyes (29.7%), was stable in 25 eyes (67.6%), and

154    deteriorated in 1 eye (2.7%). The mean $\pm$ standard deviation CRT decreased significantly

155    from $342.3 \pm 111.6$ μm (range, 130–677) at baseline to $196.6 \pm 55.4$ μm (range, 112–323)

156    at 1 year ($P < 0.001$) (Fig. 1b). One year after the first IVA, the OCT images showed that

157    the retinal exudative changes had resolved in 27 eyes (73.0%) and remained in 10 eyes

158    (27.0%).

159    ICGA images were available at baseline and at 3 months and 1 year after treatment.

160    Because of allergy to ICGA, the ICGA images were unavailable at 1 year for one of the 37

161    patients. At baseline, all eyes had at least 1 polypoidal lesion on the ICGA images. Three

162    months after the first injection, ICGA showed that the polypoidal lesions had resolved in

163    17 eyes (45.9%); at 1 year, the polypoidal lesions had resolved in 19 eyes (51.4%). Of the

164    eyes in which the polypoidal lesions had resolved at 3 months, the lesions recurred in 1

165    eye at 1 year.The total number of injections during the first year ranged from 7 to 12

166    (mean, 8.2; median, 7). The number of visits was the same as the number of injections

167    during the first year because all patients were examined and treated at the same time. The

168    intervals between injections at 1 year ranged from 4 to 12 weeks (mean, 9.7; median, 12).

169    The distributions of the intervals between injections at 1 year were 4 weeks in 11 eyes

170    (29.7%), 6 weeks in 1 eye (2.7%), 8 weeks in 2 eyes (5.4%), 10 weeks in 1 eye (2.7%),

171    and 12 weeks in 22 eyes (59.5%) (Fig. 2).

172    Twenty-two eyes (59.5%) had no recurrence after 3 monthly injections, whereas 15

173    eyes (40.5%) had a poor response or recurrence, ie, a poor response to IVA in 3 eyes and

174    at least 1 recurrence in 12 eyes. We compared the changes in the BCVA and CRT between

175    the eyes with no recurrence and the eyes with a poor response or recurrence (Fig. 3). The

176    mean BCVA improved in both groups until 6 months after the first injection. The eyes

177    with no recurrence had improvements in the mean BCVA at 1 year. However, a

178    significantly greater decrease in the mean BCVA occurred in the eyes with a poor response

179    or recurrence than in the eyes with no recurrence ($P < 0.05$) (Fig. 3a). Of the 12 eyes with

180    recurrence, although the retinal exudative changes had resolved in 5 eyes at 1 year, the

181    BCVA did not improve significantly in these eyes at 1 year ($P = 0.940$). At 1 year, a

182    significantly greater decrease in CRT occurred in the eyes with no recurrence than in the

183    eyes with a poor response or recurrence ($P = 0.001$) (Fig. 3b). Figures 4 and 5 show

184    representative cases.

185        We evaluated factors predictive for patients who could not continue to extend the

186    treatment intervals because of a poor response to IVA or recurrence of PCV. Table 1

187    shows the results of the multivariate logistic regression analysis. The number of polyps at

188    baseline was associated with a poor response or recurrence of PCV (OR, 2.237; 95% CI,

189    1.034–4.843; $P = 0.041$). This result indicated that a large number of polyps at baseline

190    might be associated with patients who cannot continue to extend treatment intervals

191    during the first year of a treat-and-extend regimen.

192

193                        **Discussion**

194        In the current study, we administered IVA for PCV patients according to a treat-and-

195    extend regimen and found that this approach improved the BCVA and retinal exudative

196    changes. Furthermore, 62.2% of the patients extended the intervals of both visits and

197    injections to up to 10 weeks or longer. Yamamoto et al treated PCV with bimonthly fixed

198    dosing of IVA and reported improvement in the mean BCVA (logMAR) from 0.31 ± 0.32

199    to 0.17 ± 0.28, reduction of the mean CRT from 315 ± 146 μm to 204 ± 115μm, and

200    resolution of the retinal exudative changes in 71.1% of patients. The mean numbers of

201    visits and injections at 1 year were 12 and 7.1, respectively [24]. In the current study,

202    using a treat-and-extend regimen, we observed an improvement in the mean BCVA

203    (logMAR) from 0.37 ± 0.37 to 0.21 ± 0.29, reduction in the mean CRT from 342.3 ±

204    111.6 μm to 196.6 ± 55.4 μm, and resolution of the retinal exudative changes in 73.0% of

205    the patients. The mean numbers of visits and injections at 1 year were both 8.2. These

206    results indicated that the degree of improvement in the BCVA, CRT, retinal exudative

207    change, and number of injections with a treat-and-extend regimen is comparable to those

208    with a bimonthly fixed dosing regimen. Regarding the number of visits, the treat-and-

209    extend regimen resulted in a lower number of visits than did the bimonthly fixed dosing

210    regimen.  It should be noted that the mean treatment interval at 1 year was 9.7 weeks and

211    the percentage of patients whose treatment interval was 10 weeks or longer was 62.2%

212    and that of patients whose treatment interval was 12 weeks was 59.5%. Hikichi et al

213    treated 85 PCV patients with ranibizumab injection using a PRN regimen for 1 year and

214    reported that 28% of the patients did not require any additional injections after the 3 initial

215    monthly injections [25]. Since a treat-and-extend regimen requires injection of the eyes at

216    each follow-up visit regardless of the disease activity, their result suggests that the treat-

217    and-extend regimen may have led to overtreatment of approximately 30% of the patients

218    in our study. Further study with a longer observation period is required to evaluate

219    whether a treat-and-extend regimen is effective in extending the treatment interval

220    more and in decreasing the patient and physician burdens.

221       The percentage of patients in whom the treatment interval increased to 12 weeks at

222    1 year (59.5%) was higher than that in previous studies of treat-and-extend regimens. In

223    the Lucentis Compared to Avastin Study (LUCAS), the percentage of patients in whom

224    the treatment interval increased to 12 weeks at 1 year was 25.1% with bevacizumab and

225    37.1% with ranibizumab [20]; in the Treat-and-Extend Protocol in Patients with Wet Age-

226    Related Macular Degeneration (TREX-AMD), the percentage of patients was 26% with

227    ranibizumab [21]. There are 2 possible explanations for the discrepancies among these 3

228 studies. The first is the differences in the pharmacologic action of anti-VEGF drugs used

229 in these studies. Although bevacizumab and ranibizumab block the VEGF-A isoform only,

230 aflibercept binds to both VEGF-A and B isoforms and to placental growth factor [26, 27].

231 The binding affinity of aflibercept to VEGF is reportedly substantially higher than that of

232 ranibizumab, and aflibercept potentially has a longer intravitreal half-life relative to other

233 anti-VEGF agents [10]. Indeed, in the VEGF Trap-Eye: Investigation of Efficacy and

234 Safety in Wet AMD (VIEW) study, aflibercept was as effective as ranibizumab in

235 improving the VA in patients with AMD, but required fewer injections to achieve the

236 same effect [28]. The second explanation is the differences in the subtypes of the target

237 diseases included in the 3 studies. Although LUCAS and TREX-AMD included patients

238 with AMD without distinguishing among the subtypes, the current study included patients

239 with PCV only. Differences in the therapeutic response of AMD subtypes to anti-VEGF

240 therapy remain controversial. Although some studies have indicated that PCV is refractory

241 to anti-VEGF therapy [29, 30], a recent study found that dry maculas were seen

242 significantly less frequently in patients with typical AMD than in patients with PCV [31].

243 Further studies are required to clarify the role of the AMD subtypes in the therapeutic

244 effect of anti-VEGF therapy using a treat-and-extend regimen.

245   The current study found that the degree of improvement in BCVA was smaller in

246 patients with a poor response or recurrence, ie, patients who could not continue to extend

247 the treatment interval, than it was in patients without recurrence at 1 year (Fig. 3). This

248 result corroborates the results of a previous study of a PRN regimen that showed that

249 patients with at least 1 recurrence had significantly worse BCVA than did patients without

250 a recurrence [32]. In the current study, 12 of the 37 eyes had at least 1 recurrence. Of

251  these, the retinal exudation had resolved completely in 5 eyes at the final examination.

252  Interestingly, despite complete resolution of the exudative changes, the BCVA did not

253  improve significantly in any of these 5 eyes. This result is consistent with that of a

254  previous study that found that intravitreal ranibizumab injections with a PRN regimen did

255  not improve the BCVA significantly in AMD eyes with a recurrence, even in cases in

256  which the exudation resolved completely [33]. These findings indicate the importance of

257  avoiding a recurrence after initial resolution of the exudation with anti-VEGF drugs to

258  improve vision. Therefore, proactive treatment regimens are considered more appropriate

259  than reactive treatment regimens such as PRN regimens.

260  The multivariate analysis showed that the presence of a larger number of polyps at

261  baseline predicted a poor response or recurrence of PCV. There was also a trend toward a

262  greater percentage of a poor response or recurrence of PCV in those with remaining

263  polypoidal lesions after the 3 initial monthly injections; however, this did not reach

264  statistical significance. Recent studies have indicated that the features of polypoidal

265  lesions are important predictors of the therapeutic efficacy of anti-VEGF drugs in PCV.

266  Some studies have reported that polyps with smaller diameters are associated with

267  successful regression of exudation and no recurrence, whereas other studies have reported

268  that the regression of polypoidal lesions is related directly to fluid resolution [34–36].

269  Because the current results showed smaller BCVA improvements in patients with a poor

270  response or recurrence than in those without a recurrence, special considerations that

271  include reductions in the extended period after resolution of the retinal exudation might be

272  required in patients with a large number of polyps.

273    The current study was limited by its small sample size, retrospective nature, and lack

274    of a control group. The period of 1 year might be too short to accurately assess treatment

275    effectiveness and perform comparisons with other treatment regimens. In addition, other

276    treatment options for PCV such as PDT were not considered. Further prospective studies

277    with larger sample sizes and longer follow-up periods should clarify the efficacy of IVA

278    using a treat-and-extend regimen to treat PCV.

279

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395 **Figure Legends**

396 **Fig. 1 a** Mean changes in best-corrected visual acuity (BCVA) from baseline in 37 eyes

397 treated with aflibercept using a treat-and-extend regimen. **b** Mean changes in central

398 retinal thickness (CRT) from baseline in 37 eyes treated with aflibercept using a treat-and-

399 extend regimen. Error bars: standard error of the mean. *$P < 0.001$

400

401 **Fig. 2** Distributions of the treatment intervals at 1 year

402

403 **Fig. 3 a** Mean changes in best-corrected visual acuity (BCVA) from baseline between

404 polypoidal choroidal vasculopathy (PCV) eyes with no recurrence and those with a poor

405 response to IVA or recurrence. **b** Mean changes in central retinal thickness (CRT) from

406 baseline between PCV eyes with no recurrence and those with a poor response to IVA or

407 recurrence. The circles indicate eyes with no recurrence; the squares indicate eyes with a

408 poor response to IVA or recurrence. *$P < 0.05$

409

410 **Fig. 4** An 80-year-old woman with polypoidal choroidal vasculopathy in her right eye

411 responded well to the treat-and-extend regimen and did not have recurrences during the 1-

412 year follow-up. **a** At baseline, indocyanine green angiography (ICGA) showed a

413 polypoidal lesion (arrow) and a branching network (arrowheads). **b** Optical coherence

414 tomography (OCT) showed subretinal fluid (arrow) and protrusion of the retinal pigment

415 epithelium (RPE) due to a polypoidal lesion (arrowhead). The best-corrected decimal

416 visual acuity was 0.4. **c** Three months after the first aflibercept injection, ICGA showed

417 complete regression of the polypoidal lesions. **d** OCT showed resolution of the subretinal

418    fluid and RPE protrusion. The visual acuity was 0.6. **e, f** At 1 year, ICGA and OCT

419    showed complete regression of the polypoidal lesions and exudative changes. The

420    injection interval at the final visit was 12 weeks and the visual acuity was 0.9

421

422    **Fig. 5** An 81-year-old man with polypoidal choroidal vasculopathy in his right eye

423    responded to intravitreal aflibercept injections but had a recurrence with extension of the

424    interval between injections. **a** At baseline, indocyanine green angiography (ICGA) showed

425    polypoidal lesions (arrows) and a branching network (arrowheads). **b** Optical coherence

426    tomography (OCT) showed subretinal fluid (arrow) and protrusions of the retinal pigment

427    epithelium due to polypoidal lesions (arrowheads). The best-corrected decimal visual

428    acuity was 0.9. **c, d** Three months after the first aflibercept injection, ICGA and OCT

429    showed complete regression of the subretinal fluid and polypoidal lesions. The visual

430    acuity was 1.2. **e** At 9 months, when the interval between injections was extended to 10

431    weeks, OCT showed recurrence of the subretinal fluid (arrows) and protrusions of the

432    retinal pigment epithelium (arrowheads). The visual acuity was 0.5. The interval was

433    shortened by 2 weeks. **f, g** One year after the first aflibercept injection, when the interval

434    between injections was 4 weeks, ICGA and OCT showed regression of the polypoidal

435    lesions and subretinal fluid. However, the visual acuity was still 0.6

436

437

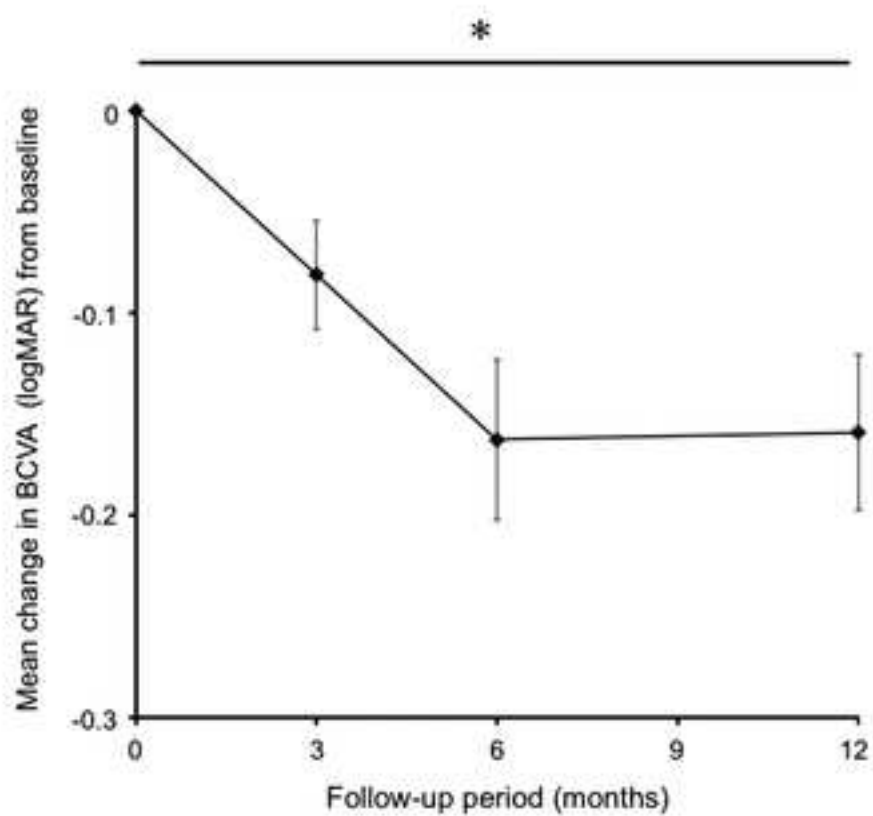**Table 1** Multivariate logistic regression analysis of factors associated with poor response or recurrence of PCV

| | | No recurrence | Poor response or recurrence | Multivariate logistic regression analyses[a] | |
|---|---|---|---|---|---|
| | | | | OR (95% CI) | P |
| Age, mean ± SD | | 73.9 ± 9.0 | 72.5 ± 8.5 | 0.969 (0.854–1.099) | 0.622 |
| LogMAR BCVA, mean ± SD | | 0.44 ± 0.29 | 0.27 ± 0.46 | 0.474 (0.024–9.421) | 0.624 |
| CRT (μm), mean ± SD | | 364.5 ± 130.9 | 309.7 ± 66.5 | 0.994 (0.982–1.007) | 0.352 |
| GLD on FA (μm), mean ± SD | | 3978 ± 1746 | 3117 ± 1228 | 0.999 (0.998–1.000) | 0.130 |
| GLD on ICGA (μm), mean ± SD | | 2517 ± 1085 | 2302 ± 746 | 1.000 (0.998–1.002) | 0.677 |
| Number of polyps, mean ± SD | | 2.5 ± 1.4 | 3.5 ± 2.0 | 2.237 (1.034–4.843) | 0.041 |
| Size of largest polyp, mean ± SD | | 258 ± 120 | 301 ± 132 | 1.009 (1.000–1.018) | 0.063 |
| Regression of polyps at 3 months | Yes, n (%) | 13 (59.1%) | 4 (26.7%) | 4.756 (0.549–41.237) | 0.157 |
| | No, n (%) | 9 (40.9%) | 11 (73.3%) | 1.000 (Reference) | - |

*LogMAR BCVA* logarithm of the minimum angle of resolution best-corrected visual acuity, *CRT* central retinal thickness, *GLD* greatest linear dimension, *FA* fluorescein angiography, *ICGA* indocyanine green angiography, *OR* odds ratio, *CI* confidential interval, *SD* standard deviation

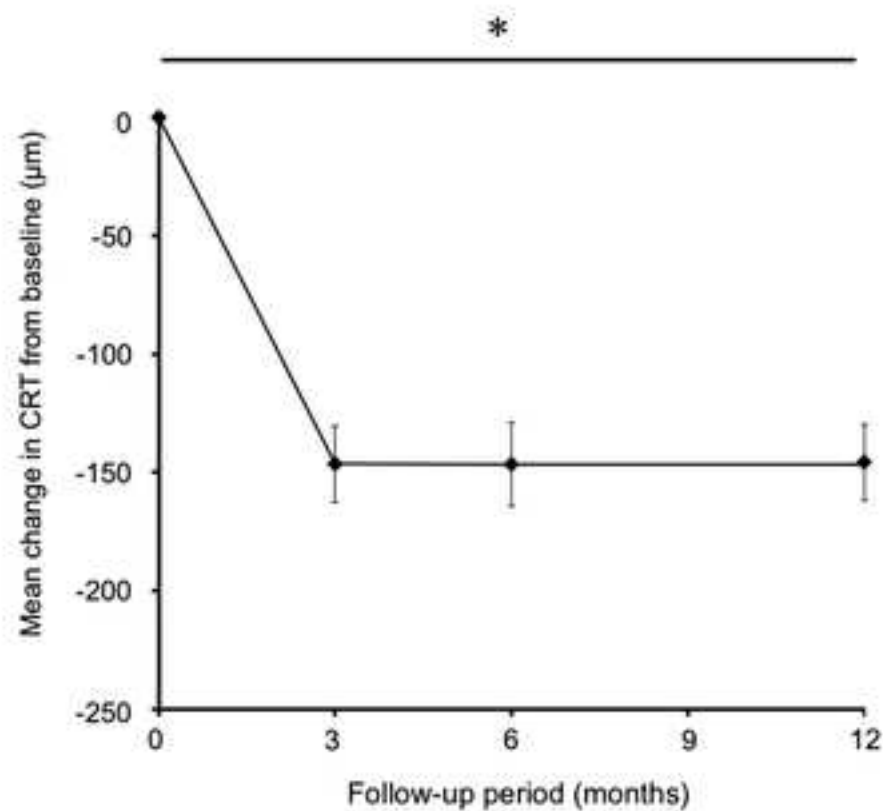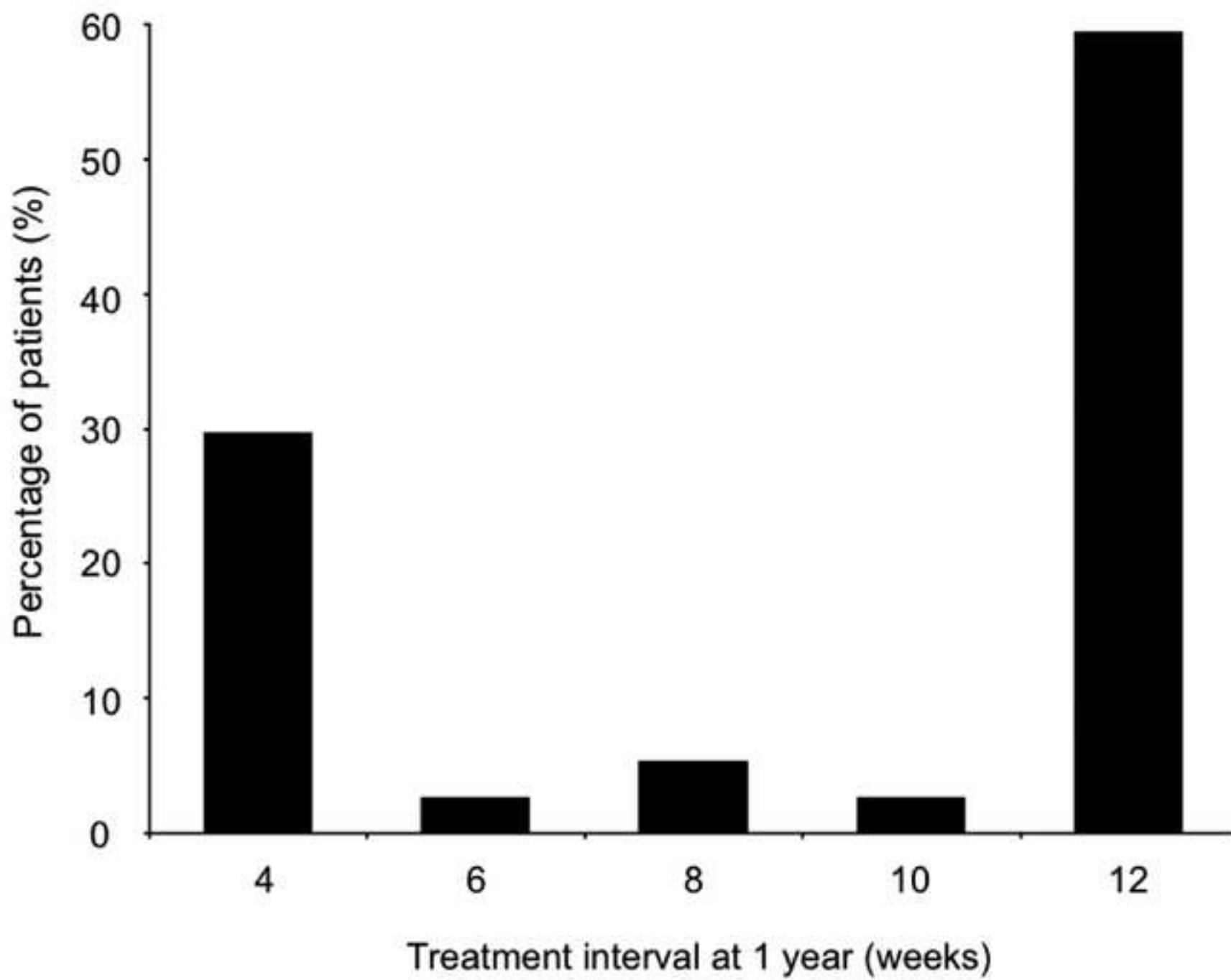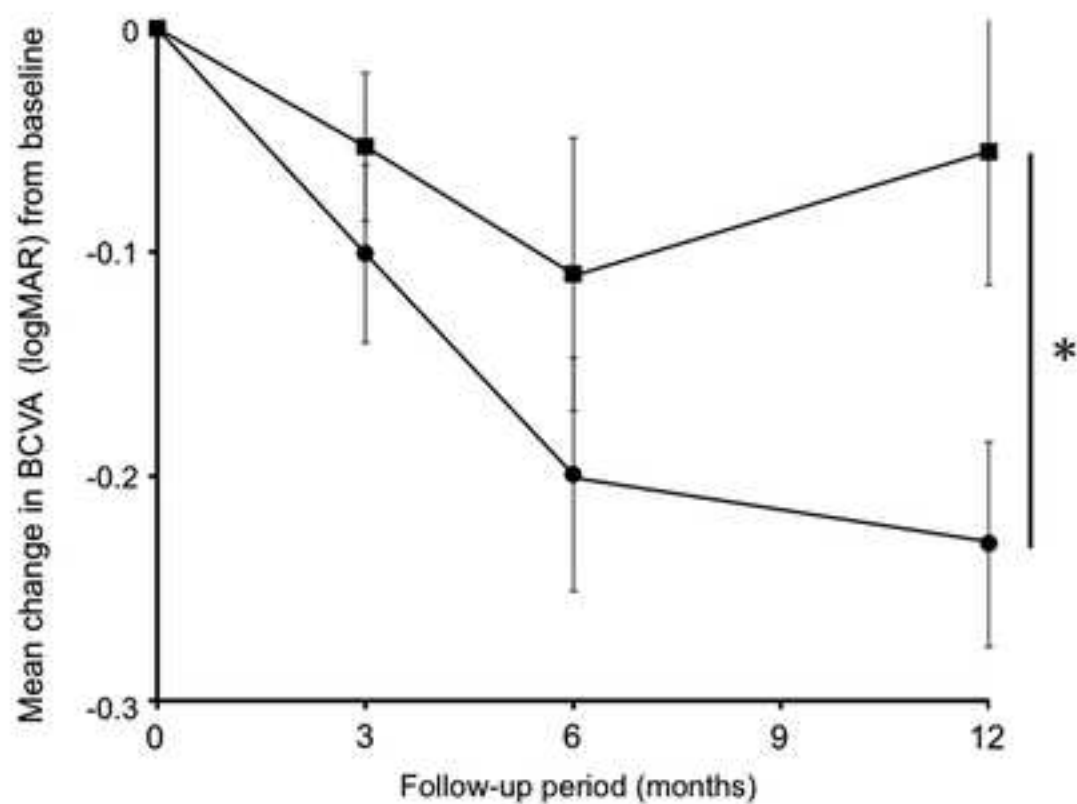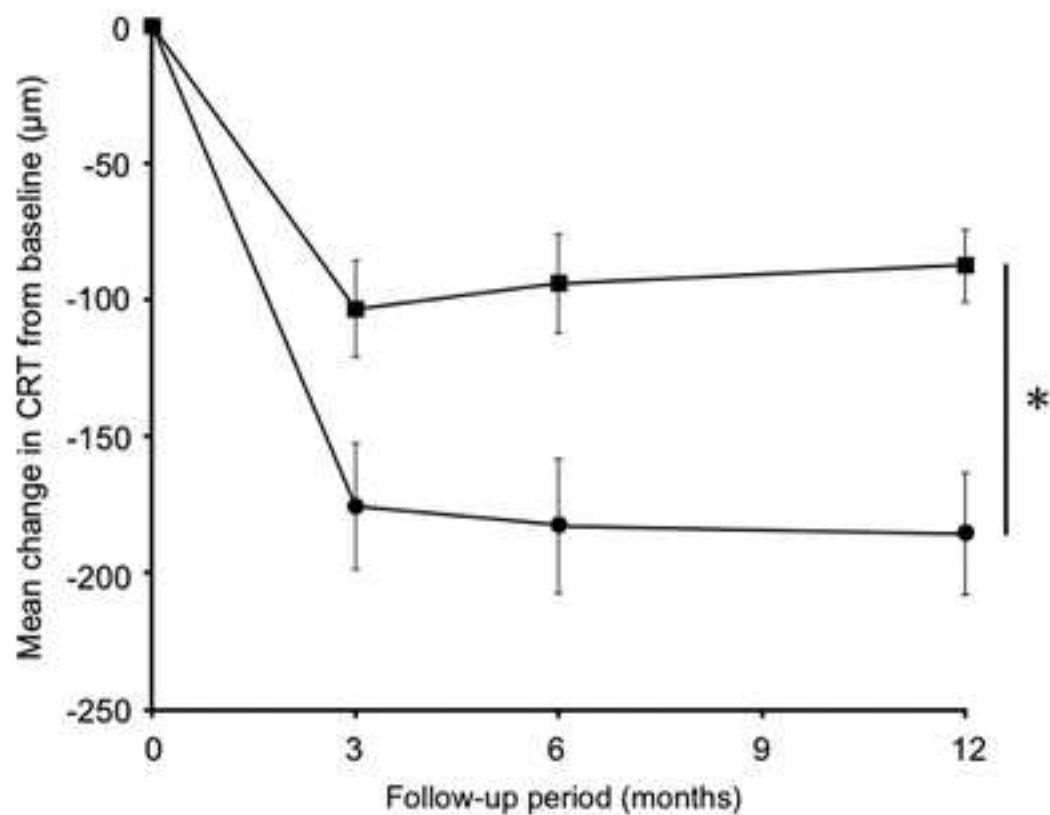[a]Adjusted by all factors listed in this table.

Figure1

# Figure 1

Figure 2

Figure3

# Figure 3

a



b

Figure4

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# Figure 4

Figure5 Click here to download Figure Fig 5.tif ⬇

## Figure 5