Treatment of Retinal Angiomatous Proliferation in Age-Related Macular Degeneration

A Series of 104 Cases of Retinal Angiomatous Proliferation

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Objective: To report the management of retinal angiomatous proliferation (RAP), a recently described intraretinal neovascular lesion occurring in age-related macular degeneration.

Methods: This was a retrospective review of consecutive patients with age-related macular degeneration who underwent treatment of RAP from January 1, 2000, through January 31, 2003. Inclusion criteria were age 55 years or older, signs of age-related macular degeneration, and diagnosis of RAP based on dynamic indocyanine green angiography. Baseline angiograms were reviewed and RAP was classified into the following 3 stages: stage 1, intraretinal neovascularization, early stage; stage 2, subretinal neovascularization, middle stage; and stage 3, choroidal neovascularization, late stage. Treatment and concomitant treatment results were assessed separately for each RAP stage. The clinical data were statistically analyzed (χ² test and analysis of variance) for 2 main outcome measures—complete obliteration of the lesion and final visual acuity.

Results: Eighty-one patients (99 eyes) with 104 RAPs were identified. Forty-two lesions were at stage 1, 42 at stage 2, and 20 at stage 3. The following 5 treatments were performed: direct laser photocoagulation of the vascular lesion, laser photocoagulation of the feeder retinal arteriole, scatter “gridlike” laser photoagulation, photodynamic therapy, and transpupillary thermotherapy. Complete obliteration of RAP was achieved in about 24 (57.1%) of the stage 1 lesions (direct laser photocoagulation of the vascular lesion, 73% success rate; photodynamic therapy, 45%), 11 (26.2%) of the stage 2 lesions (scatter gridlike laser photocoagulation, 38% success rate; direct laser photocoagulation of the vascular lesion, 17%), and only 3 (15.0%) of stage 3 lesions (P = .001). Predictive factors with a significant effect on final visual acuity were initial visual acuity (P = .003) and early lesion stage (P = .04). Best final visual acuity was 0.41 (mean, direct laser photocoagulation of the vascular lesion in stage 1) and 0.39 (mean, photodynamic therapy in stage 1), with a mean decrease of 2.5 and 3 lines from baseline, respectively.

Conclusions: Treatment of RAP remains difficult. Early detection of the lesion and subsequent direct conventional laser photocoagulation seems to be associated with better anatomical and functional outcome. Once the vascular complex is well established, anatomical closure is rarely achieved. Further study is warranted to assess the long-term efficacy and the need for re-treatment.


Retinal vascular anomalous complex and retinal choroidal anastomosis are terms that have been used interchangeably in the past decade to identify a peculiar vascular abnormality of the macula in age-related macular degeneration (AMD). It was originally suggested that in advanced AMD proliferation of the retinal capillaries could eventually lead to intraretinal neovascularization with no connections to the choroidal vasculature. Advances in fundus imaging and recent histopathologic correlations have increased our knowledge of the retinal vascular anomalous complex and have validated the original assumption of Hartnett et al. Dynamic indocyanine green angiograms (ICGA) showed retinal arteries feeding and retinal veins draining the vascular complex in more than 90% of cases of retinal vascular anomalous complex. Intraretinal and subretinal neovascularization but not choroidal neovascularization (CNV) were the most consistent findings of the histopathologic work of Lafaut et al. Yannuzzi et al revisited this subject in an extensive article on these lesions, which supported the original concept of retinal angiomatous proliferation, thus suggesting the acronym RAP as the best representative description of the disease.

Retinal angiomatous proliferation may occur frequently, possibly representing one fourth of occult CNV detected at fluores-
cein angiography. We lack information about the natural course of RAP because these lesions have often been interpreted as occult CNV. However, it has been reported, and it is also our experience, that most patients achieve final visual acuity (VA) of 20/200 or worse because of a disciform scar.

The most appropriate treatment for these lesions is unknown. Laser photocoagulation has been suggested in a small series of RAP or in cases in which the presumptive diagnosis was occult CNV with “hot spot.” Inasmuch as dynamic ICGA was not used routinely to evaluate eligible patients, the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) and Verteporfin in Photodynamic Therapy (VIP) trials could have also enrolled patients who likely had RAP and not CNV. Although we have no information from these clinical trials about the use of photodynamic therapy (PDT) for the treatment of RAP, it has been reported that PDT is of little benefit in these lesions. We describe our experience with the treatment of 104 RAPs in 81 consecutive patients (99 eyes) with AMD.

METHODS

We obtained approval to conduct this retrospective study from the institutional review boards of the 2 study centers. Medical records of all patients with AMD who underwent treatment of RAP at our institutions between January 1, 2000, and January 31, 2003 were reviewed.

The inclusion criteria for diagnosis of RAP were age 55 years or older; signs of AMD, including hard and soft drusen, mottling of the retinal pigment epithelium, and retinal pigment epithelial detachment and atrophy; diagnosis of RAP based on dynamic ICGA (temporal evidence of “dye filling of at least one retinal arteriole descending into the deep retinal space to a vascular communication and at least one draining retinal vein”). We excluded from the study patients with any condition other than AMD associated with CNV, such as degenerative myopia, angioid streaks, infectious or inflammatory choroidal diseases, tumors, inherited disorders, or trauma.

Each patient underwent a complete ocular examination when first seen and during follow-up, including slitlamp biomicroscopy, best-corrected VA at manifest refraction using a standard Snellen chart, fundus biomicroscopy (78-diopter [D] lens; Volk Optical Inc, Mentor, Ohio), and simultaneous dynamic fluorescein and ICGA with a scanning laser ophthalmoscope (HRA Engineering, Heidelberg, Germany). The instrument was set at 6 frames per second, and the dyes were given as an antecubital injection of a 2-mL mixed solution of 2.5 mL of 20% sodium fluorescein and 25 mg of indocyanine green, followed by a saline solution flush. For consistency, 2 of us (F.B. and G.S.) retrospectively reviewed all of the baseline angiograms and classified RAP into 3 stages, according to Yannuzzi et al. In brief, stage 1 involved proliferation of intraretinal capillaries originating from the deep retinal complex (intraretinal neovascularization, early stage; Figure 1). Stage 2 was determined by growth of the retinal vessels into the subretinal space (subretinal neovascularization, middle stage; Figure 2). Stage 3 occurred when CNV could clearly be determined angiographically (late stage; Figure 3). Stereoscopic viewing of selected images was often used for classification.

Treatments differed according to RAP stage (Tables 1, 2, and 3) and were chosen at the discretion of the treating ophthalmologist. Data were collected about the 5 types of treatment used:

1. Direct laser photocoagulation of the vascular lesion (LPhc; argon green, 532 frequency-doubled Nd:YAG lasers). The treatment was performed according to the Macular Photocoagulation Study parameters for classic extrafoveal CNV (Table 1 and Figure 1 and Figure 2).
2. Laser photocoagulation of the feeder retinal arteriole (FVT; argon green, 532 frequency-doubled Nd:YAG lasers). Spots at least 50% larger than the feeder vessel, 0.2-second to 0.5-second duration, were applied during multiple sessions, 15 days apart, to constrict or obliterate the feeder vessel (Tables 1 through 3).
3. Scatter “gridlike” laser photocoagulation (GRID; argon green, 532 frequency-doubled Nd:YAG lasers). Scatter (GRID) burns consisted of light to moderately intense (gray) photocoagulation burns of 0.1-second duration, 100-µm spot size, spaced approximately 2 burn widths from each other and applied for 3 rows around a spared central area of 1500 µm centered in the fovea (Tables 1 through 3; Figure 3).
4. Photodynamic therapy. Photodynamic therapy with verteporfin was used according to the recommended standard procedure (Tables 1 through 3; Figure 3).
5. Transpupillary thermotherapy (TTT; 2 consecutive spots of subthreshold 810-nm diode laser, 3-mm and 1.2-mm spot size, 400-mW and 200-mW intensity, respectively, 1-minute exposure) (Tables 1 through 3).

The selected treatment and concomitant results (success or failure) were assessed separately for each RAP stage (ie, 1 through 3). The final VA and status of the eye were recorded as the date that the patient was last evaluated. Snellen VA was used for functional outcomes; it was converted to a logarithm of the minimal angle of resolution algorithm only to convert to a line score to record the number of lines gained or lost after treatment.

For this study, one RAP was considered as one case, and all RAPs per cases diagnosed at baseline were included and used for data
analyses. Clinical data were statistically analyzed (StatGraphics; Statistical Graphics Corp, StatPoint Inc, Herndon, Va) to obtain 2 main outcomes—complete obliteration of the lesion and final VA. The occurrence of obliteration in the different stages and among the different treatments was compared using the \( \chi^2 \) test. An association between pretreatment variables (initial VA and RAP stage) as well as treatment and final VA was examined using multifactor analysis of variance. \( P \leq .05 \) was considered statistically significant.

RESULTS

One hundred four RAPs were diagnosed in 81 patients (99 eyes) and were treated at the 2 study centers between January 1, 2000, and January 31, 2003. Demographic data and baseline characteristics are summarized in Table 4. At baseline, 63 patients had only 1 RAP; multiple RAPs in the same eye were detected in 5 patients and bilateral RAPs were present in 17 patients.

All patients underwent complete follow-up of at least 6 months for analyses of the 2 outcome measures. Mean follow-up for RAP stage 1 was 18 months, for stage 2 was 22 months, and for stage 3 was 20 months (\( P = .27 \)). During follow-up, new RAPs developed in 23 (23%) of 99 eyes; 10 RAPs were diagnosed in the fellow unaffected eye after a mean of 18.3 months from baseline (range, 3-36 months), and 13 new RAPs developed in the affected eye.

Tables 1 through 3 list the final outcomes for the 3 stages of RAP. Overall, RAP was successfully obliterated in about 24 (57.1%) stage 1 lesions (intraretinal neovascularization, early stage), 11 (26.2%) stage 2 lesions (subretinal neovascularization, middle stage), and 3 (15%) stage 3 lesions (CNV, late stage; Figure 4, \( \chi^2 = 13.63; P = .001 \)). Direct laser photocoagulation (22 RAPs) and PDT (11 RAPs) were the treatments most frequently performed in stage 1 (Table 1). Well-developed RAPs (stage 2) were treated with all of the treatments examined, with the following frequency (Table 2). Photodynamic therapy was the most frequently performed treatment in stage 3 RAP, and GRID and FVT were used with the same frequency (Table 3).

There was no significant difference in the obliteration rate among the various treatments within each stage group of RAP. However, in stage 1 (Table 1), LPhc of the vascular lesion achieved complete obliteration of RAP in 16 (73%) of 22 cases after a mean follow-up of 17.4 months (range, 6-48 months). All of the vascular complexes were extrafoveal at baseline and only 1 treatment session was necessary for complete closure (Figure 1). Mean final VA was 0.41 (range, 0.005-1.0), with a mean decrease of 2.5 lines from baseline. Ten (45%) of the patients in this group maintained a final VA of 0.5 or bet-

Figure 2. Stage 2 retinal angiomatous proliferation. Angiograms obtained with fluorescein (A) and indocyanine green (B) in a 74-year-old woman with decreased visual acuity (0.2) in the left eye for 2 months. Dynamic indocyanine green angiogram revealed a well-developed extrafoveal retinal vascular anomalous complex with 1 feeding retinal arteriole and more draining retinal veins, with telangiectatic capillaries in the surrounding area. Late fluorescein phases showed cystoid macular edema with a foveal macracyst. Three months after direct laser photocoagulation of the vascular lesion (LPhc; argon green, 532 frequency-doubled Nd:YAG lasers), dynamic fluorescein (C) and indocyanine green (D) angiograms of the left eye showed complete obliteration of the vascular complex within the postlaser atrophic scar. There were transmission defects in the fovea and the surrounding area, but the cystoid macular edema and the macracyst were completely reabsorbed. Visual acuity in the left eye remained stable (0.2) for 13 months. Twenty-two months after treatment, visual acuity decreased to 0.06 OS. Fluorescein and indocyanine angiograms demonstrated diffuse remodeling of the subfoveal choriocapillaris with massive cystoid macular edema (E) and a retinochoroidal anastomosis (F).
The second most successful treatment was PDT, with a closure rate of 43% (5 of 11 RAPs) but functional results similar to those in the LPhc group: the mean final VA was 0.39 (range, 0.005-1.0), with a mean decrease of 3 lines from baseline, and 5 (45%) of the patients maintained a final VA of 0.5 or better.

**Table 1. Stage 1 RAP: Final Outcomes**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RAP, No. (%) (N = 42)</th>
<th>Complete Obliteration of RAP, No. (%)</th>
<th>Visual Acuity*</th>
<th>Mean Follow-up, mo</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial, Mean</td>
<td>Final, Mean</td>
</tr>
<tr>
<td>LPhc</td>
<td>22 (52)</td>
<td>16 (73)</td>
<td>0.53</td>
<td>0.41</td>
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<tr>
<td>FVT</td>
<td>2 (5)</td>
<td>1 (50)</td>
<td>0.01</td>
<td>0.20</td>
</tr>
<tr>
<td>GRID</td>
<td>6 (14)</td>
<td>2 (33)</td>
<td>0.45</td>
<td>0.12</td>
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<tr>
<td>PDT</td>
<td>11 (26)</td>
<td>5 (45)</td>
<td>0.49</td>
<td>0.39</td>
</tr>
<tr>
<td>TTT</td>
<td>1 (2)</td>
<td>0</td>
<td>0.70</td>
<td>0.40</td>
</tr>
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</table>

Abbreviations: FVT, laser photoagulation of feeder retinal arteriole; GRID, scatter “gridlike” laser photoagulation; LPhc, direct laser photoagulation of vascular lesion; PDT, photodynamic therapy; RAP, retinal angiomatous proliferation; TTT, transpupillary thermotherapy.

*Snellen chart.

**Table 2. Stage 2 RAP: Final Outcomes**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RAP, No. (%) (N = 42)</th>
<th>Complete Obliteration of RAP, No. (%)</th>
<th>Visual Acuity*</th>
<th>Mean Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial, Mean</td>
<td>Final, Mean</td>
</tr>
<tr>
<td>LPhc</td>
<td>12 (29)</td>
<td>2 (17)</td>
<td>0.49</td>
<td>0.25</td>
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<tr>
<td>FVT</td>
<td>5 (12)</td>
<td>1 (20)</td>
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<td>0.09</td>
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<tr>
<td>GRID</td>
<td>13 (31)</td>
<td>5 (38)</td>
<td>0.26</td>
<td>0.10</td>
</tr>
<tr>
<td>PDT</td>
<td>9 (21)</td>
<td>1 (11)</td>
<td>0.25</td>
<td>0.13</td>
</tr>
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<td>TTT</td>
<td>3 (7)</td>
<td>2 (67)</td>
<td>0.12</td>
<td>0.15</td>
</tr>
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</table>

Abbreviations: FVT, laser photoagulation of feeder retinal arteriole; GRID, scatter “gridlike” laser photoagulation; LPhc, direct laser photoagulation of vascular lesion; PDT, photodynamic therapy; RAP, retinal angiomatous proliferation; TTT, transpupillary thermotherapy.

*Snellen chart.

**Table 3. Stage 3 RAP: Final Outcomes**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RAP, No. (%) (n = 20)</th>
<th>Complete Obliteration of RAP, No. (%)</th>
<th>Visual Acuity*</th>
<th>Mean Follow-up, mo</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Initial, Final</td>
<td>≥0.5, No. (%)</td>
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<tr>
<td>LPhc</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>FVT</td>
<td>5 (25)</td>
<td>1 (20)</td>
<td>0.14</td>
<td>0.11</td>
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<tr>
<td>GRID</td>
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<td>2 (40)</td>
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<td>0.07</td>
</tr>
<tr>
<td>TTT</td>
<td>1 (5)</td>
<td>0</td>
<td>0.12</td>
<td>0.02</td>
</tr>
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</table>

Abbreviations: FVT, laser photoagulation of feeder retinal arteriole; GRID, scatter “gridlike” laser photoagulation; LPhc, direct laser photoagulation of vascular lesion; NA, not applicable; PDT, photodynamic therapy; RAP, retinal angiomatous proliferation; TTT, transpupillary thermotherapy.

*Snellen chart.

Figure 3. Stage 3 retinal angiomatous proliferation. Simultaneous angiograms obtained with fluorescein (A) and indocyanine green (B and C) in an 80-year-old woman with decreased visual acuity (0.16) in the right eye for 4 months. B and C, Indocyanine green angiograms revealed retinochoroidal anastomoses with an evident choroidal neovascular component. D, Twenty-two months after 1 photodynamic therapy treatment and 1 scatter “gridlike” laser photoagulation treatment, fluorescein angiogram showed a still active disciform scar. Final visual acuity was 0.005 OD.
In stage 2 (Table 2), complete closure of the vascular complex was achieved in 2 (17%) of 12 RAPs after LPhc treatment, compared with 5 (38%) in the GRID group and 1 (11%) in the PDT treatment groups (Figure 2). Overall, the mean final VA was 0.16, with a mean loss of 5 lines at last follow-up examination. Only 2 patients had a final VA of 0.5 or better.

In stage 3 (Table 3), the anatomical and functional results were discouraging (Figure 3). Overall, obliteration of RAP was achieved in 3 (15%) of 20 patients, and the mean final VA was poor (≤0.1), with a mean loss of 3.3 lines at last follow-up examination. No patients had a final VA of 0.5 or better. An association between initial VA (P=.003) as well as stage of RAP (P=.04) and final VA was established using multifactor analysis of variance. In other words, eyes with higher VA and stage 1 RAP at baseline had better VA at the end of follow-up period (Figure 5). Again, within each stage group of RAP, no association was found between a specific treatment method and better final VA.

Our data underline the importance of the early detection of RAP, which can be successfully treated at early stages. The most appropriate treatment of RAP is unknown, mainly because of the diagnostic problems encountered with these lesions when using conventional angiography. The technical gap was responsible for the lack of information on prevalence and natural history of the retinal vascular complex. We think that this form of neovascular AMD is not uncommon, possibly representing as much as one fourth of occult or minimally classic CNV.6,10 Although data on the natural history of RAP are missing, there is a general consensus toward a poor functional prognosis with these lesions, after progression to different stages and a resulting disciform scar.2-4,9,11

We reviewed the data for various treatments according to specific clinical characteristics at baseline (ie, RAP stage). The rationale for the treatments chosen at the discretion of the treating ophthalmologist deserves some explanation. The lack of information published in the literature regarding the treatment of RAP lesions prompted us to select 5 types of treatment.

Direct laser photocoagulation of the neovascular process is a standardized treatment for CNV.16 RAP, being initially by nature extrafoveal, may be a suitable indication for use of LPhc (Table 1 and Figure 1). Photodynamic therapy has been recently proposed for treating classic or occult CNV,12-14 thereby representing another reasonable treatment option (Tables 1 through 3). It has been also recently reported that PDT is of little benefit in RAP.15 However, baseline VA was poor in that series (mean, 20/126), suggesting an advanced stage of the lesions at baseline.

Figure 4. Obliteration rate in retinal angiomatous proliferation (RAP) stages 1 through 3 (χ²=13.6; P=.001).

Figure 5. Mean±Tukey Honestly Significant Difference intervals (95% confidence interval) for final visual acuity with various stages of retinal angiomatous proliferation (P=.04). Asterisk indicates the mean.
Although the exact pathogenesis of RAP has not been elucidated, advanced Bruch membrane changes, always present in patients with RAP, seem to be the common precursor.3 One assumption is that in AMD thick deposits within Bruch membrane and loss of choroidal vessel may lead to less available oxygen.3 Resultant hypoxia of the outer retinal layers may in turn up-regulate the release of angiogenic growth factor, such as vascular endothelial growth factor.20,21 In transgenic mice, overexpression of the vascular endothelial growth factor causes new vessel proliferation originating from the deep retinal capillary plexus with extension into the subretinal space. In time, the neovascular lesion gradually enlarges and coalesces with other vascular complexes,22,23 thereby resembling the clinicopathologic changes of RAP in human eyes reported by others.3,6-9 If hypoxia of the outer retinal layer has a role in the development of RAP, then scatter GRID laser photocoagulation of the macula has a rationale, either because it may enable the choriocapillaris to deliver oxygen to ischemic inner retina24 or because removal of some of the photoreceptors reduces the metabolic needs of the outer retina (Tables 2 through 4).25,26

Transpupillary thermotherapy is being investigated as a possible treatment for “occult” subfoveal CNV.27 The modified TTT technique used in our study (2 consecutive, superimposed, subthreshold spots of 3 and 1.2 mm) is based on the thermotolerance mechanism of tissue hyperthermia.28 It has proved to be well tolerated by the retina and showed encouraging results in the treatment of stage 2 and 3 RAP (Tables 2 through 4).17

The most significant finding of our study is that RAP of recent onset may be amenable to conventional thermal laser treatment. This is consistent with treatment suggestions of previous studies reporting on similar lesions.3,4,9 In our series, RAP at earlier stages showed better closure rates (Figure 1; P = .001). In addition, 2 factors were significantly related to better final VA: initial VA (P = .003) and earlier stage of lesions (P = .04).

Initial VA depends on the integrity of the macular photoreceptors and, therefore, on the duration of the disease. The relationship between initial VA and stage of RAP and final VA is not surprising. Early treatment may lead to better anatomical and functional outcome. Of 42 RAPs at stage 1, 24 (57.1%) were successfully obliterated (Table 1 and Figure 4). The success rate decrease to 26.2% (11 of 42 lesions) at stage 2 (Table 2 and Figure 4) and 15.0% (3 of 20 lesions) at stage 3 (Table 3 and Figure 4). The final VA was also significantly different among patients with stage 1 RAP and stage 2 or 3 RAP (Figure 5).

It seems that once the vascular complex is well established, anatomical closure is rarely achieved either with LPhc, FVT, PDT, TTT, or GRID. In addition, new RAPs developed in almost one fourth of eyes during follow-up, either in the fellow eye or the same eye. Hence, early diagnosis is important.

With conventional angiography, images are usually captured at 1 frame per second. That makes virtually impossible visualization of the progression of the dye through the vascular complex, even though images are taken at very early phases (Figure 6). By contrast, with dy-
This retrospective review describes various treatment methods being used to treat RAP of varying levels of activity and duration. This study has many limitations. Its retrospective nature may lead to biased enrollment; this is why we classified patients as having either early or more advanced disease and we examined the various treatments separately within each group. The low cell counts in some subgroups in each stage could have been responsible for the lack of association between a specific treatment and a better closure rate or final VA within the 3 stages of RAP. Therefore, we do not know, for example, whether scatter GRID or TTT would be successful at earlier stages of RAP development. In addition, VA was measured using a Snellen chart, as opposed to the more standardized Early Treatment Diabetic Retinopathy Study chart, and duration of follow-up is short.

Nevertheless, RAP is becoming an important cause of neovascular AMD, and more cases will be diagnosed with the advent of dynamic ICGA. Treatment of these lesions remains a difficult problem to be solved. Our data cast light on the different treatments for the various stages of the vascular complexes. Despite several treatment options, early intervention with direct conventional laser photocoagulation of an extramacular RAP is the only treatment advised for best long-term visual outcome. Further study is warranted to assess the long-term efficacy and the need for re-treatment.

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REFERENCES


CONCLUSIONS

Dynamic ICGA (up to 12 frames per second), the progressive filling of the lesion enables detection of very small and recent-onset RAP. That is possibly why in the series of Yannuzzi et al the diagnosis of RAP was made at stage 1 (intraretinal neovascularization) in only 41% of the eyes and a retinal-retinal anastomosis was seen in stage 1 in only 30% of the eyes. The higher sensitivity of high-speed dynamic angiography in the early diagnosis of RAP is also supported by the low prevalence of retinal pigment epithelial detachments, a late complication of RAP, recorded in our patients (12.5%).