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Late Stage III Retinal Angiomatous Proliferation with Retino-Choroidal Anastomosis do not Respond Well to Treatment with Ranibizumab (Lucentis®)

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Abstract

Background: Retinal Angiomatous Proliferations (RAP) is a subgroup of exsudative or "wet" Age-related Macular Degeneration (wAMD) with devastating reduction of visual acuity in later stages. Intravitreal Ranibizumab provides a good therapy, but is considered to be not as effective in this class of neovascularization compared to choroidal neovascularization (CNV). We investigated the efficacy of Ranibizumab in late stage III RAP with retino-choroidal anastomosis compared to the outcome of CNV lesions.

Methods: Retrospective analysis of the data of all for wAMD with Ranibizumab treated patients. Patients were divided into groups depending on the lesion type into RAP (identified and selected clinically, proven by fluorescein angiography) and CNV types (identified by fluorescein angiography only) named occult, minimally and predominantly classic groups. Best-corrected visual acuity (BCVA) was obtained before ("diagnosis"), during (1st, 2nd and 3rd injection) and after upload ("1st control").

Results: Before first injection the visual acuity decreased in all groups (0.73 to 0.78 logMAR for all CNV, 0.95 to 1.02 logMAR for RAP). During upload there is no further decline in visual acuity but no improvement as well up to the 1st control visit in the RAP group (1.02 to 1.03 logMAR), but a statistically significant increase in all other groups (0.78 to 0.67 logMAR).

Conclusion: Clinically identified late stage III RAP lesions with retino-choroidal anastomosis respond worse to treatment with monthly Ranibizumab than all other lesion types regardless of their severity. Treatment results in stabiliziation of visual acuity, but – in contrast to other forms of CNV – no further improvement. Therefore, patients with this special form need to be identified and treated as early as possible.

Keywords: Retinal angiomatous proliferation; Age-related macular degeneration; Ranibizumab; Choroidal neovascularization

Introduction

Retinal Angiomatous Proliferations (RAP) is a subgroup of neovascularization occurring in exsudative (or "wet") age-related macular degeneration (wAMD). Normally, neovascularisation starts from the choroid ("choroidal neovascularization", CNV) and grows upwards breaking through Bruch's membrane and towards the retinal pigment epithelium. Some remain hidden below ("occult" CNV), some extending through the pigment epithelium below the neurosensory retina to a different amount ("classic" CNV), causing exsudation, bleeding, fibrosis and severe vision loss. There are mixed forms which might then be further classified by the area of classic or occult lesion into "minimally classic" with <50% of lesion area to be above the pigment epithelium and predominantly classic with >50% of lesion above the pigment epithelium.

RAP has been described for the first time by Hartnett et.al. [1] in 1992. Later they have been described as neovascularization growing the opposite way, beginning in the retina (hence the name which was coined by Yannuzzi et al. in 2001 [2]) and ending up forming anastomosis with the choroid.

According to Yannuzzi there are three different stages to be differentiated by angiography [3] which has been supported by histopathological examinations [4]. In stage I there are new vessels formed in the inner retinal plexus (intraretinal neovascularization). They can be found by angiographic leakage at the end of retinal vessels. Those vessels grow deep into the retina (subretinal neovascularization), where they cause detachment of the neurosensory retina (stage IIA) or the retinal pigment epithelium (stage IIB). In stage III (chorioretinal anastomosis) there has formed an anastomosis between the retinal and the choroidal vessel system normally causing extreme leakage and devastating vision loss. Untreated, this condition leads to subretinal fibrosis and scarring which cannot be treated nowadays.

Gass et al. [5] or Scott and Bressler [6] provide an alternative process of formation of retino-choroidal anastomosis which they call "retinal anastomosis to the lesion" (RAL) and state that the formation of a choroidal lesion precedes that of the final proliferation of retinal vessels to the deep lesion.

Both theories have in common the formation of a retino-choroidal anastomosis with high blood flow, strong leakage and severe vision loss. The percentage of RAP causing wAMD ranges from 8 to 25% [6]. RAP have been reported to have a poor prognosis [7,8] and a high tendency towards symmetry and bilaterality. Gross et al. [9] showed bilateral affection in 56% after 2 years and 100% after 3 years in contrast to 43% bilaterality after 5 years in other CNV types [10].

The therapy strategies used in the past were numerous and included conventional laser photocoagulation [11,12], photodynamic therapy [13-15], surgery [16-19] or combinations [16,20], all with more or less discouraging outcomes.

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Only with introduction of anti-vascular endothelial growth factor drugs (VEGF) the results are slightly more promising, both with Bevacizumab (Avastin®) [21-23] and Ranibizumab (Lucentis®) [24]. Still, RAP seems to be an aggressive form of neovascularization.

We wanted to find out the outcome of ranibizumab treated late stage III RAP with retino-choroidal anastomosis – identified clinically – in a clinical setting and compare this outcome to other forms of choroidal neovascularization.

Materials and Methods

Patient consent

Written and informed consent for treatment was obtained from all patients treated.

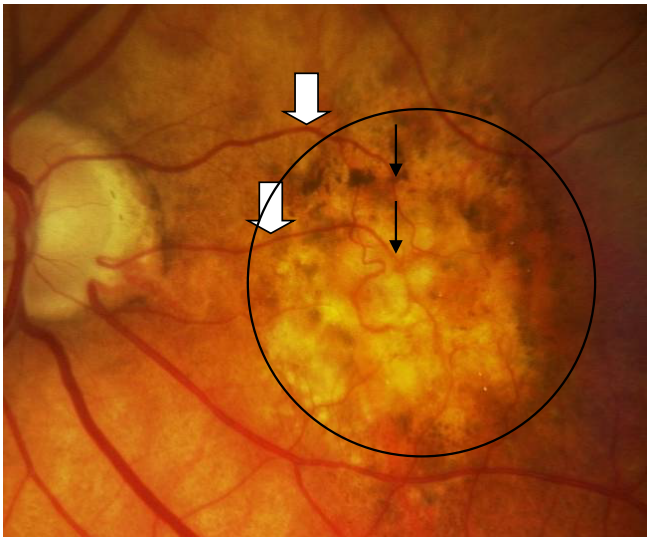

Figure 1: Example of clinical diagnosis of RAP. This figure shows all inclusion criteria: dilated vessels in the macular region (hollow arrow), going down deep into the retinal tissue (slim arrow) in or near the center of the lesion (circle).

Patient selection

Between February 2007 and October 2013 so far 2201 eyes of 1879 patients started or completed initial monthly loading dose treatment with Ranibizumab 0.5 mg intravitreally for wAMD in our clinic.

For the RAP group we selected those eyes of the patients that showed clinical signs of RAP which were defined as:

- Dilated retinal vessels in the macular region which
- Went down deep into the retinal tissue
- In or near the center of the exsudative lesion (e.g. Figure 1)

20 eyes of 20 patients met these criteria (RAP group). It is important to note that there were no angiographic definitions of RAP included, although the selected eyes have had fluorescein angiography which proved the presence of retina-choroidal anastomosis.

Of the 2201 eyes that started treatment and were not identified as clinically recognizable RAP, 1026 had completed all visits up to at least the 1st control visit after 3rd injection, all needed visual acuity data were available and a fluorescein angiography was performed and was useful to classify the CNV type lesions into occult, minimally or predominantly classic. Patients without fluorescein angiography, fluorescein angiography that did not allow classifying the lesion type without doubt or without a complete data set consisting of visual acuity at all times (diagnosis of wAMD, 1st, 2nd and 3rd injection and 1st control visit) were not included. These patients were used as compare groups depending on the type of neovascularization (occult, minimally classic or predominantly classic) (Figure 2).

The time between diagnosis and 1st treatment ranged between 4 days and two month and was noted but not evaluated.

Clinical identification of RAP is only possible in late stage III. Therefore it might be confounding to compare those late stages with other neovascularizations in earlier stages. So of all identified CNV we selected the subgroup with similar visual acuity out of occult, minimally and predominantly classic lesions as compare groups. As the best visual acuity in RAP group was 0.2 decimal, we selected those patients for the

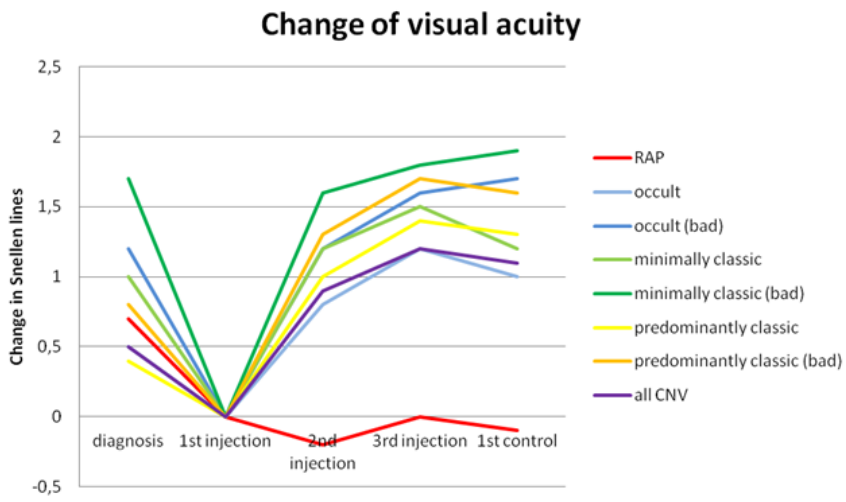

Figure 2: Change of visual acuity during treatment. Shown here for better and more intuitive visualization are the changes in Snellen lines in the different groups. Therefore no error bars are given. For the logMAR changes and standard deviation please refer to Table 1.

subgroups with similar low visual acuity (≤ 0.2 decimal) and named the groups "bad".

Table 1 summarizes the data of the groups. There were no statistically significant differences between the groups regarding age or gender, although the RAP group had a gender shift towards more female.

Visual acuity measurement

Visual acuity was measured with best correction using numbers due to the completely clinical setting. So we refer to "best corrected visual acuity" simply by "visual acuity" throughout this paper. The smallest line in which at least 60% of the numbers were read correctly was set the visual acuity and noted decimal.

Treatment

Patients were diagnosed to have wAMD on an outpatient basis examination. Although most of them were referred to our clinic by other ophthalmologists who presumed the disease, we chose the term "diagnosis" to refer to this timepoint. Due to different reasons which include different insurance covering and different insurance procedures as well as the need to obtain written consent before the injection, the first treatment ("1st injection") was given at another timepoint. The time in between ranges from days to month. As this might heavily confound the results of treatment, we chose "1st injection" as baseline. The "2nd injection" and "3rd injection" were given 4 and 8 weeks after the 1st. The "1st control" visit was scheduled 4 to 6 weeks after the 3rd injection. If there was still lesion activity, further treatments were planned but not evaluated.

Injection procedure

The injection was done following the regulations and suggestions given by the German ophthalmologic association (Deutsche Ophthalmologische Gesellschaft, DOG) and the Association of Ophthalmologists (Berufsverband der Augenärzte Deutschlands, BVA) which can be found on their respective homepages. Written consent was obtained before start of treatment.

Group	RAP		Occult		Occult (bad)		Minimally classic		Minimally classic (bad)		Predominantly classic		Predominantly classic (bad)		All CNV	
n (eyes)	20		764		451		74		53		188		130		1026	
Gender	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Female	14	70	457	60	260	58	44	59	30	57	105	56	77	59	606	59
Male	6	30	307	40	191	42	30	41	23	43	83	44	53	41	420	41
Age																
Average	78.4		76.8		78.3		77.8		78.2		76.2		76.6		76.8	
Minimal	64		45		45		52		52		52		54		45	
Maximal	92		98		98		96		96		94		94		98	
Visual acuity	**logMAR**	**Std. dev.**	**logMAR**	**Std. dev.**	**logMAR**	**Std. dev.**	**logMAR**	**Std. dev.**	**logMAR**	**Std. dev.**	**logMAR**	**Std. dev.**	**logMAR**	**Std. dev.**	**logMAR**	**Std. dev.**
Diagnosis	0.95	0.35	0.71	0.37	0.92	0.30	0.78	0.36	0.92	0.31	0.80	0.36	0.96	0.29	0.73	0.37
1st injection	1.02	0.40	0.76	0.40	1.04	0.27	0.88	0.43	1.09	0.31	0.84	0.37	1.04	0.26	0.78	0.40
2nd injection	1.04	0.35	0.68	0.40	0.92	0.33	0.76	0.41	0.93	0.35	0.74	0.40	0.91	0.35	0.69	0.40
3rd injection	1.02	0.40	0.64	0.42	0.88	0.36	0.73	0.42	0.91	0.35	0.70	0.41	0.87	0.36	0.66	0.42
1st control	1.03	0.33	0.66	0.39	0.87	0.34	0.76	0.37	0.90	0.32	0.71	0.39	0.87	0.35	0.67	0.39
Average change in Snellen lines compared to baseline (1st injection)																
Diagnosis	0.7		0.5		1.2		1.0		1.7		0.4		0.8		0.5	
1st injection	0.0		0.0		0.0		0.0		0.0		0.0		0.0		0.0	
2nd injection	-0.2		0.8		1.2		1.2		1.6		1.0		1.3		0.9	
3rd injection	0.0		1.2		1.6		1.5		1.8		1.4		1.7		1.2	
1st control	-0.1		1.0		1.7		1.2		1.9		1.3		1.7		1.1	
Statistical significancy																
***in* the groups compared to baseline (1st injection); double-sided Student's t-test for paired variables**																
Diagnosis	0.3340		<0.0001		<0.0001		0.0003		<0.0001		0.0402		0.0011		<0.0001	
1st injection	not done		not done		not done		not done		not done		not done		not done		not done	
2nd injection	0.6750		<0.0001		<0.0001		0.0010		0.0004		<0.0001		<0.0001		<0.0001	
3rd injection	0.9290		<0.0001		<0.0001		0.0004		0.0005		<0.0001		<0.0001		<0.0001	
1st control	0.8880		<0.0001		<0.0001		0.0007		<0.0001		<0.0001		<0.0001		<0.0001	
***between* the RAP and respective CNV groups at equal time points; double-sided Student's t-test for unpaired variables; green background for p<0.05**																
Diagnosis	not done		0.0056		0.7084		0.0544		0.7074		0.0817		0.8942		0.0105	
1st injection	not done		0.0081		0.8734		0.1655		0.5006		0.0640		0.8326		0.0145	
2nd injection	not done		0.0002		0.1508		0.0046		0.2380		0.0015		0.1474		0.0003	
3rd injection	not done		0.0005		0.1449		0.0081		0.1584		0.0024		0.1254		0.0007	
1st control	not done		0.0001		0.0465		0.0026		0.0474		0.0004		0.0463		0.0001	

Table 1: Summary of data of the treatment groups.

Statistical significancy: In the respective groups visual acuity was compared to baseline (1st injection), using double-sided Student's t-test for paired variables. Between the groups visual acuity was compared to the RAP group at the given time points, using double-sided Student's t-test for unpaired variables. A green background helps visualize the selected p<0.05 for statistical significance was met

Statistical Analysis

Data evaluated were visual acuity measurements at the given time points. The decimal visual acuity was converted into logMAR, and all subsequent mathematical procedures were done with the logMAR values. The visit of the 1st injection was selected as baseline, changes in visual acuity shown in the tables and diagrams were given in Snellen lines compared to this visit. Data were calculated using Microsoft Excel Version 2007. Student's double-sided t-test was used to calculate differences between the groups (unpaired variables) and longitudinal during treatment (paired variables). $p<0.05$ was selected to reflect statistical significance.

Results

Out of the 2201 eyes we had to exclude 1175 eyes for different reasons, including not having fulfilled the complete initial treatment and control visit, missing data of visual acuity at any of the above given time points, missing fluorescein angiography or unability to classify the lesion clearly into the above mentioned classes.

We clinically identified 20 eyes to have RAP lesion. Those eyes were examined by fluoresein angiography and the retino-choroidal anastomosis was visible. By fluorescein angiography we identified 764 eyes to have occult CNV, 74 to have minimally and 188 to have predominantly classic CNV. The age or gender do not vary statistically significant between the groups, although the RAP group tends to have a higher rate of women.

The baseline visual acuity was worst in the RAP group (0.95 logMAR). Although the other groups showed a tendency towards better visual acuity (0.78 logMAR for minimally classic, 0.80 logMAR predominantly classic), it was only statistically significant better in the overall group (0.73 logMAR) and the occult CNV lesion type group (0.71 logMAR). Therefore we created subgroups of the occult, minimally and predominantly classic groups according to the visual acuity at baseline. All patients having similar or worse visual acuity than the maximum visual acuity in the RAP group (≤ 0.2 decimal) were selected to form the "bad" groups. There is no statistical significant difference between the RAP group and the "bad" groups regarding baseline visual acuity (0.92 logMAR for bad occult, 0.92 logMAR for bad minimally classic and 0.96 logMAR for bad predominantly classic).

In all groups patients lost visual acuity to different extend due to having to wait for the 1st injection. This waiting time is due to different insurance covering and changes in procedures necessary to perform the injections during the last years. It varies widely between some days and some months. Therefore we chose the visual acuity before the 1st injection as baseline visual acuity.

All groups and subgroups except the RAP group showed statistically significant increase in visual acuity at the 1st control visit compared to the baseline (RAP: 1.02 logMAR to 1.03 logMAR, occult CNV: 0.76 logMAR to 0.66 logMAR, bad occult CNV: 1.04 logMAR to 0.87 logMAR, minimally classic CNV: 0.88 logMAR to 0.76 logMAR, bad minimally classic CNV: 1.09 logMAR to 0.90 logMAR, predominantly classic CNV: 0.84 logMAR to 0.71 logMAR and bad predominantly classic CNV: 1.04 logMAR to 0.87 logMAR).

This increase seem to depend on the lesion type and ranges roughly between 1 and 2 Snellen lines; exact data for the various time points are given in Table 1. The increase reaches statistical significance depending on the lesion type and group size during treatment or at least at the last visit (1st control) in all groups. The "bad" groups need more injections during upload to have statistically significant increase in visual acuity. The RAP group does not experience statistically significant changes in visual acuity. During treatment, the initial visual acuity might roughly be stabilized.

Discussion

RAP is an aggressive form of neovascularization in wAMD. The late stage III differs from all other forms by having established an anastomosis between the retinal and choroidal circulation. We assume that the high blood flow in such vessels, together with the very leaky vessel walls produce a high amount of leakage into intra- and subretinal as well as sub-pigment-epithelial spaces. This might account for the devastating vision loss of patients suffering from such disease.

The treatment of RAP is similar to those of other types of CNV lesions. However, the success rates are debatable. There are reports of worse outcome of RAP lesions [25-29] as well as outcomes comparable to other CNV lesion types [6,30,31].

To our knowledge there is no study trying to compare the clinically identified late stage III RAP lesions to other forms of CNV. The method used here to clinically identify RAP does have the advantage of selecting only very well established chorioretinal anastomosis with high throughput of blood flow and leakage. Another stage of RAP might not be identified clinically and is therefore not included here. As far as we are aware of there is only one study investigating the effect of ranibizumab treatment for stage III RAP [32]. It could be shown that treatment resulted in stopping progression and stabilization of visual acuity as well as central retinal thickness.

One weak point of this investigation is of course the retrospective character. We tried to overcome the flaws of missing data, patients lost to follow up, different length of inter-visit-times by very strictly defining the control groups and selecting only those patients with every needed data clearly available. Nevertheless, the weakest point is undoubtedly the selection of the RAP lesions by only clinical criteria. This raises questions as to the nature and origin of the anastomosis according to the two theories discussed earlier and later on, if all lesions would have been proven by clinically not-so-common indocyanine green angiography and possible differences in lesion size, which was not evaluated at all. On the other hand this is the first study to clinically define RAP and might provide some information as to how to treat the other eye of patients already having RAP lesion in one eye. The data presented here show that treatment of such lesions is not to be delayed. In contrast to all other forms of neovascularization, late stage RAP lesions cannot be treated to an increase of visual acuity.

As there are two theories to how those anastomosis form, it might be possible that patients were selected that initially did not have RAP, but normal CNV with an anastomosis that formed late. As the hallmark of both is the anastomosis no matter how and when it was formed we believe that this should not be biasing the investigation.

Conclusion

The data presented here suggest that clinically identified late stage III RAP lesions with retino-choroidal anastomosis respond worse to treatment with monthly Ranibizumab than all other lesion types regardless of their severity. Treatment results in stabiliziation of visual acuity, but – in contrast to other forms of CNV – no further improvement. Therefore, patients with this special form need to be identified and treated as early as possible. We suggest that patients with RAP lesion in one eye should be monitored closely and treated lavishly to prevent formation of a retino-choroidal anastomosis in the other eye.

Ethical Standards

To the best of our knowledge, this investigation does not meet the criteria to be defined as a clinical study and, hence, no ethics committee was involved. Patients gave written and informed consent for the treatment, which was started, done and completed absolutely independent and before this investigation. Data presented here have been evaluated anonymized.

Presentation at a Conference

The data of this investigation were presented at the Congress of "Deutsche Ophthalmologische Gesellschaft" 2013.

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