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Statement of the BVA, the DOG, and the RG on treatment of choroidal neovascularization in diseases other than neovascular age-related macular degeneration

Dated Ocotber 2017

Key messages

1. Choroidal neovascularizations (CNV) occur not only in age-related macular degeneration (AMD), but also in numerous other macular and retinal disorders of varying etiology and, if left untreated, can cause irreversible visual loss.
2. The diagnosis of CNV as well as the indication for treatment should be made in the same way as in neovascular AMD:
   - On initial diagnosis: best-corrected visual acuity, fundus examination, optical coherence tomography (OCT), and fluorescein angiography
   - At follow-up: best-correct visual acuity, fundus examination, OCT, and, depending on findings, fluorescein angiography
3. Active CNV should be treated with intravitreal operative medication (IVOM) using vascular endothelial growth factor (VEGF) inhibitors if patients have visual acuity of at least 0.05 or if there is sufficient reason to assume that visual acuity could increase to over 0.05 under treatment.
4. Underlying disorders can include, e. g., (only a selection is presented here):
   - High myopia
   - Angioid streaks
   - Central serous chorioretinopathy
   - Active and inactive uveitis of varying etiology, including retinochoroiditis, chorioretinitis, and choroiditis
   - Eye injuries
   - Retinal dystrophies, e. g., best disease and pattern dystrophies
   - Idiopathic CNV
   - Subretinal masses (osteomas, hamartomas, nevi)

   If CNV is not present as a complication in the above-mentioned disorders, IVOM with VEGF inhibitors should not be performed.
5. Ranibizumab and aflibercept are approved in Germany for the treatment of CNV secondary to pathologic myopia.
6. Ranibizumab has been approved in Germany since 12/2016 for the treatment of CNV in disorders other than neovascular AMD and pathologic myopia irrespective of the underlying disease. The other VEGF inhibitors, aflibercept and bevacizumab, can be used off-label.
7. Due to its overall significantly poorer treatment results, photodynamic therapy (PDT) should only be used in exceptional cases and extrafoveal localization.
8. After one initial intravitreal administration of VEGF inhibitors, further CNV activity should be monitored monthly for the first 6 months (see point 2). In the case of persisting or recurrent activity, repeated IVOM should be performed. Depending on disease course, the follow-up interval might be extended 6 months after the last IVOM. In individual justified cases

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(e. g., patients requiring frequent re-injections), a different treatment regimen (e. g., treat and extend) can be considered in the further course.
9. If visual acuity drops below 0.05 on anti-VEGF treatment, or no further positive treatment outcome is expected (e. g., in the presence of atrophy and/or fibrosis), treatment should be discontinued, unless there is a clear possibility that visual acuity could increase again to over 0.05 under treatment.
10. If no improvement is seen under therapy with a certain VEGF inhibitor, or if deterioration occurs, one can consider switching to an alternative VEGF inhibitor.

1 Introduction

In addition to age-related macular degeneration (AMD), there are numerous other retinal diseases of varying etiology that can be associated with choroidal neovascularizations (CNV). As in AMD, severe irreversible visual loss can occur if left untreated.

The following article discusses examples of the more common underlying diseases.

1.1 High myopia

High myopia is generally defined as a refractive error of ≥−6 diopters spherical equivalent or an axial length ≥ 26.5 mm. A distinction must be made from pathologic myopia, which is additionally characterized by typical fundus lesions, e. g., myopic cracks, chorioretinal atrophy, and pigment changes [1].

Population-based studies estimate the incidence of high myopia in Europe to be approximately 2.7%, with increasing incidence and prevalence at a younger age [2, 3]. A dependence on ethnicity is apparent, with a higher prevalence among Asians compared with Caucasians [4]. Other factors that appear to be associated with myopia include urban environment and higher education levels [5].

There are currently no reliable figures on the frequency of pathologic myopia in Germany. Up to 3.2% of Asian populations exhibit myopia-induced pathological fundus changes [6]. It is assumed that approximately 5–10% of patients with pathologic myopia develop CNV [1]. From this, one can estimate an overall prevalence of approximately 0.2% in the total population for Europe/Germany. The natural disease course is often unfavorable, involving progressive loss of visual acuity, particularly in the case of subfoveal CNV [7]. Compared with AMD, the affected group is younger and often still in working age, meaning that, if left untreated, considerable socioeconomic effects are associated with this complication. Overall, CNV secondary to myopia is considered the commonest cause of vision loss in young people aged ≤50 years [1].

1.2 Angioid streaks

Angioid streaks (AS) is a descriptive term for reddish-brown lines visible on fundoscopy, which are typically circular around the optic disc, from where they radiate into the periphery [8]. The term originates from their similarity to vessels on fundoscopy. Histopathologically, AS are small breaks in Bruch's membrane. There are numerous underlying systemic diseases that can be associated with AS. With an estimated prevalence of 1:25,000–100,000, pseudoxanthoma elasticum (PXE) is the most frequent of these diseases [9]. However, AS also occurs in other disorders, such as PXE-like syndromes, e. g., generalized arterial calcification of infancy (GACI), various hemoglobinopathies, e. g., β-thalassemia and sickle cell anemia, as well as Paget's disease in rare cases [8]. As long as the retinal pigment epithelium and the photoreceptors are intact, AS generally have no serious effects on patients' vision. However, they predispose to the development of CNV, which manifests in the majority of patients in the disease course [10]. CNV secondary to AS are typically classic membranes (type 2). If left untreated, these CNV often have a poor prognosis due to their aggressiveness and foveal involvement and generally result in significant, irreversible loss of visual acuity [8]. Since AS-related diseases are usually systemic diseases, the interdisciplinary treatment of patients, e. g., in collaboration with internists, plays an important role. However, it has been shown that vision impairment, at least with regard to PXE patients, had the greatest impact on quality of life compared with other comorbidities [11]. For further information, the reader is referred to the statement from the DOG, RG, and BVA on the treatment of choroidal neovascularization in PXE.

1.3 Central serous chorioretinopathy

Central serous chorioretinopathy (CSC) is a relatively common disease of the ocular fundus, which results in localized serous detachment of the neurosensory retina in the macular region, often accompanied by focal detachment of the retinal pigment epithelium [12]. Another characteristic feature frequently seen is an increased choroidal thickness, indicating that the choroid may play an important pathogenetic role [13]. The disease typically affects younger male patients [14]. A link to increased stress levels [12], as well as the systemic use of glucocorticoids, has been described [15]. Due to the positive effects sometimes observed for aldosterone receptor antagonists, mineralocorticoid receptor involvement is also discussed [16].

In general, the acute form of CSC is a self-limiting disease that improves spontaneously within around 3–4 months [17]. It is important to distinguish this form from chronic CSC, in which persistent angiographic leakage in the macular region, chronic subretinal fluid, pigment changes, and atrophic lesions can still be found even after 6 months. The chronic form in particular is associated with the development of CNV, which can lead to irreversible loss of vision. The incidence of CNV secondary to chronic CSC is put at 4–8% [18]. The recommendations below relate exclusively to the treatment of CSC-related CNV. Further information on CSC and its treatment can be found in a separate statement from the DOG, RG, and BVA.

1.4 Active and inactive uveitis of varying etiology, including retinochorioiditis, chorioretinitis, and chorioiditis

In principle, a multitude of intraocular inflammatory disorders are associated with the development of CNV. It occurs particularly in punctate inner choroidopathy (PIC), multifocal choroiditis, presumed ocular histoplasmosis syndrome (POHS), Vogt–Koyanagi–Harada syndrome, toxoplasmosis, and serpiginous choroiditis [19]. A study on 648 patients determined the frequency of CNV to be approximately 2%, irrespective of the underlying etiology [20]. If left untreated, the formation of CNV is associated with a poor prognosis due to the often young age of patients and the aggressive course of the disease [21–23]. The diagnosis of CNV secondary to uveitis can be hampered, for example, by concomitant inflammatory macular edema. The treatment recommendations below are explicitly intended only for cases with proven CNV. With regard to the treatment of inflammatory macular edema secondary to uveitis, the reader is referred to the relevant statement from the DOG, RG, and BVA. Furthermore, when establishing the diagnosis of CNV, a comprehensive diagnostic workup (if this has not already taken place) should be carried out to identify possible underlying diseases and, if applicable, a treatment of the underlying disease should be initiated.

1.5 Eye injuries

The development of CNV following traumatic eye injury, while rare, is potentially vision threatening. Patients in whom the choroid has ruptured in the perifoveal region, generally resulting from blunt occur trauma, are at greatest risk. The risk of developing CNV following choroidal rupture is put at approximately 5% [24]. In rare cases, lasers can also cause traumatic or iatrogenic chorioretinal injury. Pathogenetically, disruption in the region of the retinal pigment epithelium and Bruch's membrane as a result of intense laser energy likely plays a crucial role [25, 26].

1.6 Retinal dystrophies

There are a number of retinal dystrophies that, in rare cases, are associated with CNV. However, due to their rarity, no large relevant case series are available. By way of example, attention should be drawn to frequent associations with Best disease, adult vitelliform macular dystrophy, and pattern dystrophies [27–30]. In addition, CNV is often also seen in Sorsby fundus dystrophy and, if so, is associated with a relatively aggressive course [31].

1.7 Idiopathic CNV

Idiopathic CNV is defined as CNV in patients younger than 50 years once possible underlying ocular or systemic diseases have been excluded [32]. There are no reliable figures on the frequency of idiopathic CNV; however, it is a rare condition. Although the natural course of idiopathic CNV is often relatively mild compared with other entities, it is subject to considerable variability given, e. g., its sometimes extrafoveal localization [32].

1.8 Subretinal tumors

In principle, all subretinal masses can cause CNV. Hereof, CNV secondary to osteomas, sclerochoroidal calcifications, and nevi have most frequently been described. Osteomas in particular are most likely to cause structural changes in the photoreceptor–pigment epithelium complex predisposing to subsequent CNV development. Although masses as such rarely cause a reduction in visual acuity, CNV is often associated with a massive loss in visual acuity [33].

2 Treatment methods/study results

2.1 Anti-VEGF therapy

2.1.1 The RADIANCE study

The RADIANCE study [34] investigated the efficacy and safety of 0.5 mg intravitreal ranibizumab in patients with myopic CNV compared to PDT over 12 months in a randomized, double-blind, multicenter, controlled phase III study. A total of 277 patients were included and randomized to three arms:

1. Ranibizumab 0.5 mg, treatment regimen according to "stability criteria," defined as no change in best-corrected visual acuity (BCVA) compared with the two previous monthly controls.
2. Ranibizumab 0.5 mg, treatment regimen according to "disease activity criteria," defined as visual impairment due to intra- or subretinal fluid or active leakage secondary to a CNV lesion determined using OCT and/or fluorescein angiography.
3. PDT; treatment with ranibizumab was possible from the third month.

The primary endpoint was BCVA at 3 months.

- Ranibizumab therapy was superior to PDT at 3 months in terms of BCVA (group 1: +10.5 letters, group 2: +10.6 letters, group 3: +2.2 letters).
- The improvement in vision was accompanied by a reduction in central retinal thickness.
- Further improvement in visual acuity was observed at 12 months in the groups treated primarily with ranibizumab (group 1: +13.8 letters, group 2: +14.4 letters).
- Although patients in group 3, that were able to receive additional treatment with 0.5 mg intravitreal ranibizumab from month 3, subsequently showed an increase in visual acuity, they failed to reach the level of patients treated primarily with ranibizumab (+9.3 letters) at 12 months.
- Treatment monitoring by means of disease activity criteria (group 2) was not inferior to visual acuity-monitored treatment.
- Patients received on average 4.6 injections in group 1 and 3.5 injections in group 2 over a 12-month period. In all, 50.9% of patients needed 1–2 injections, 34.5% 3–5, and 14.7% 6–12 injections.
- The ocular and non-ocular safety profile was in line with ranibizumab in other indications.

2.1.2 The MYRROR study

The MYRROR study [35] investigated the efficacy and safety of 2 mg intravitreal aflibercept in patients with myopic CNV in a multicenter, randomized, double-blind, controlled phase III study. A total of 122 patients were included and randomized to two arms:

1. Aflibercept 2 mg, re-injections according to activity criteria at monthly follow-up (visual acuity, retinal thickness, intra-/subretinal fluid, CNV activity, bleeding, at examiner's discretion); if criteria were negative, a sham injection was performed.
2. Monthly fixed sham injection. From week 24, treatment with 2 mg aflibercept as in group 1.

The primary endpoint was BCVA at 24 weeks.

- At 24 weeks, treatment with aflibercept proved superior to sham injections in terms of BCVA (group 1: +12.1 letters, group 2: –2 letters).
- At 48 weeks, a further improvement in visual acuity (+13.5 letters) was seen in the patient group treated primarily with aflibercept (group 1).
- Although patients in the group that were able to receive treatment with aflibercept from week 24 (group 2) also showed an increase in visual acuity (+3.9 letters) at 48 weeks, they did not reach the level of patients treated primarily with aflibercept.
- The improvement in vision was accompanied by a reduction in central retinal thickness.
- On average, 4.2 injections were administered in group 1 and 3.0 injections in group 2 over a 12-month period.
- The ocular and non-ocular safety profile was in line with aflibercept treatment in other indications.

2.1.3 The MINERVA study

The MINERVA study [36] investigated the efficacy and safety of 0.5 mg intravitreal ranibizumab in patients with CNV due to diseases other than AMD and myopia. The study was a multicenter, double-blind, randomized, controlled phase III study. A total of 178 patients with a variety of underlying diseases were included. Patients were randomized to two groups:

1. Ranibizumab 2 mg, re-injections according to activity criteria at monthly follow-up (visual acuity, retinal thickness, intra-/subretinal fluid, CNV activity, bleeding, at examiner's discretion); if criteria were negative, a sham injection was administered.
2. Monthly fixed sham injection. From month 2, treatment with 0.5 mg ranibizumab as in group 1.

The primary endpoint was BCVA at 2 months.

- At 2 months, the ranibizumab-treated group showed significantly better results in terms of BCVA compared with the sham treatment group (group 1: 9.5 letters, group 2:–0.4 letters).
- Once it became possible to use ranibizumab in group 2 from month 2, an increase in visual acuity (+9.3 letters) was seen at 12 months, which reached the level of patients treated primarily with ranibizumab (group 1: +11 letters).
- The improvement in vision was accompanied by a reduction in central retinal thickness.
- The two groups received a comparable number of injections (group 1: 5.8, group 2: 5.4).
- The ocular and non-ocular safety profile was in line with ranibizumab treatment in other indications.

2.1.4 Other studies

In addition to these three approval trials, numerous other studies on the treatment of CNV in diseases other than AMD have been conducted using various VEGF inhibitors. However, these are mostly retrospective case series or case reports with low evidence levels. Therefore, the following are only a few examples of larger studies that have yielded additional information. For further information, the reader is referred to the statements of the DOG, RG, and BVA on the treatment of myopic CNV and CNV in pseudoxanthoma elasticum.

With regard to myopic CNV, and in addition to the studies on ranibizumab and aflibercept mentioned above, smaller randomized controlled trials have also been published that compared the treatment of CNV with bevacizumab and PDT [37] and PDT and laser coagulation [38]. Treatment with bevacizumab proved to be superior to the other treatments. Based on a large meta-analysis, the efficacy of bevacizumab appears to be comparable to that of ranibizumab [39].

There are numerous case series, some of which are prospective but most of which are retrospective, on bevacizumab for other indications. Here again, good efficacy that appears similar to that of ranibizumab was generally seen, e. g., in angioid streaks [8], CSC-related CNV [40, 41], inflammatory CNV [19], and idiopathic CNV [40, 42]. With regard to aflibercept, there are at present primarily isolated case reports that similarly point to good efficacy [41, 43, 44]. An open-label phase I/II study has also been published on the treatment of CNV secondary to POHS, demonstrating the efficacy of aflibercept treatment in POHS-related CNV with two different treatment strategies [45].

2.2 Photodynamic therapy

Based on the results of the VIP study, verteporfin is approved in Germany for the treatment of subfoveal CNV in myopia [46]. Although the study showed that PDT is able to stabilize visual acuity, improvements in vision were rarely observed. Based on the results of the RADIANCE study (see above), PDT therapy was clearly inferior to ranibizumab. Therefore, PDT is no longer recommended as a first-line treatment in myopic CNV. PDT is currently not approved for the treatment of CNV in diseases other than AMD and myopia. However, based on individual case series, a stabilization of vision also appears to be possible here [8, 42, 47–50]. PDT can be considered if CNV is in a clear extrafoveal location. However, improvements in visual acuity in line with those reported for VEGF inhibitors were rarely observed [51]. Good functional results were seen for CSC-related CNV in particular [52, 53]. Combining PDT with a VEGF inhibitor

could potentially also be beneficial in this setting [54]. However, there are no large studies in this regard to date. Therefore, on the whole, PDT should also not be recommended as a first-line treatment for these indications.

3 Treatment recommendations

3.1 Diagnosis and indication

In addition to visual acuity testing (BCVA with undilated pupils and under standardized conditions) and fundus examination in mydriasis, the fluorescein angiograph (FAG) forms the central basis for the detection and documentation of CNV in retinal diseases other than AMD. Therefore, an FAG must be carried out (except in the case of known fluorescein allergy) prior to all initial treatments in order to document the treatment indication (see brief statement from the DOG, RG, and BVA on performing and indicating IVOM). In addition, spectral-domain (SD)-OCT should also be performed prior to all initial treatments and is not only of great value for the initial diagnosis but also as an important parameter for treatment monitoring during follow-up examinations.

In addition to the diagnosis of CNV, the precise differential diagnosis of underlying diseases is of particular importance in this patient group. This is particularly relevant since, in many cases, interdisciplinary care and treatment of the underlying disease is required.

Follow-up examinations should include BCVA, a fundus examination in mydriasis, and SD-OCT. In unclear cases, a repeated FAG is also recommended.

Follow-up examinations should take place monthly after the last IVOM for a period of at least 6 months. Thereafter, "scarring" of the CNV can be clinically assumed and follow-up intervals extended where appropriate depending on findings.

3.2 Treatment approaches

Ranibizumab and aflibercept (see above) as well as PDT (subfoveal location of the CNV) are currently approved in Germany for the treatment of CNV in myopia on the basis of relevant approval studies. However, due to significantly better results on comparison, treatment with ranibizumab or aflibercept is essentially preferred over PDT.

Ranibizumab has been approved in Germany since 12/2016 for the treatment of CNV in the setting of disorders other than neovascular AMD and pathological myopia irrespective of the underlying disease. The other VEGF inhibitors, aflibercept and bevacizumab, can be used off-label. When doing so, the basic requirements for the use of off-label drugs described in previous statements by the BVA, DOG, and RG must be fulfilled.

Due to the often highly varying individual responses to VEGF inhibitor therapy and possible disease inactivity following only one initial treatment, one should start with a one IVOM. Further lesion activity is then monitored on the basis of subsequent monthly follow-ups. In the case of persistent or renewed morphologically visible lesion activity, repeated IVOM is performed in each instance.

More than 6 months following the last IVOM, follow-up examinations can be carried out at longer intervals where appropriate. In justified individual cases (e. g., patients requiring frequent re-injections), a different treatment regimen (e. g., treat and extend) can be considered in the further course.

If CNV is concomitant to angioid streaks, the particular aggressiveness of the disease and the need for more IVOM needs to be taken into account. Therefore, if CNV occurs, persists, or recurs in angioid streaks, a series of three IVOMs may be indicated.

The criteria for repeat IVOM are based on the recommendations for the treatment of neovascular AMD:

1. Subretinal fluid (OCT)
2. Persistence or increase in diffuse retinal thickening
3. Increased intraretinal cystoid fluid (OCT)
4. Increased pigment epithelial detachment (OCT)
5. New sub- or intraretinal bleeding (fundoscopy)
6. De novo reduction in visual acuity due to CNV

In unclear cases, a FAG can also be performed, with the detection of active CNV serving as a criterion for re-injection.

If patients fail to respond or further deterioration is seen during ongoing therapy with one particular VEGF inhibitor, one can consider switching to another VEGF inhibitor or, in some cases, performing a PDT. However, it should be borne in mind in such cases that this may constitute off-label use.

If visual acuity falls below 0.05 under therapy, or if morphological findings (e. g., atrophy and/or fibrosis) indicate no further positive therapeutic impact, treatment should be discontinued. In individual cases, treatment may also be indicated in visual acuity of under 0.05, assuming there is sufficient evidence to suggest that vision could increase again to 0.05 under treatment.

3.3 Performing treatment

The reader is referred here to the statement "Die Anti-VEGF-Therapie bei der neovaskulären altersabhängigen Makuladegeneration: Therapeutische Strategien" ("Anti-VEGF therapy in neovascular age-related macular degeneration: treatment Strategies"), dated November 2014, and the "Empfehlung der Deutschen Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands für die Durchführung von intravitrealen Injektionen (IVI)" ("Recommendation of the German Ophthalmological Society, the German Retina Society, and the German Professional Association of Ophthalmologists on the performance of Intravitreal Injections (IVI)").

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Compliance with ethical guidelines

Conflict of interests. See Table 1 in the Appendix.

This article does not contain any studies with human participants or animals performed by any of the authors.

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Table 1 Tabular summary of declarations of conflicts of interest

Statement on treatment of choroidal neovascularization in diseases other than neovascular age-related macular degeneration	1 Consultancy/ appraisal activities or paid collaboration on a scientific advisory board of a company in the health industry (e. g., pharmaceutical industry, medical product industry), a commercially oriented contract research organization, or an insurance company	2 Fees for lectures and training activities or paid authorships or co-authorships for a company in the health industry, a commercially oriented contract research organization, or an insurance company	3 Financial support (third-party funding) for research projects or direct financing of employees of the institution by a company in the health industry, a commercially oriented contract research organization, or an insurance company	4 Owner interest in drugs/ medical products (e. g., patent, copyright, sales license)	5 Ownership of business interests, shares, funds involving companies in the healthcare industry	6 Personal connections to an authorized representative of a company in the healthcare industry	7 Member of relevant specialist societies/ associations connected with the development of guidelines, mandate holder in guideline development	8 Political, academic (e. g., belonging to particular "schools"), scientific, or personal interests that could constitute possible conflicts	9 Current employer, relevant previous employers in the last 3 years	10 In your opinion, do all of the above points give rise to significant conflicts of interest for you or the guideline group as a whole?
Bertram, Prof. Dr. Bernd	No	No	No	No	No	No	Yes BVA: 1. Chairman, DOG: Member of the Executive Board, Spokesman for the DOG-BVA Guidelines Commission	No	Independent ophthalmologist	No
Bornfeld, Prof. Dr. Norbert	Yes Advisory Board	Yes Lecture fees	Yes Novartis clinical studies	No	No	No	Yes BVA, RG, DOG	Yes	University Hospital Essen, Germany	No
Gliem, Dr. Martin	No	Yes Bayer HealthCare, Heidelberg Engineering	Yes Bayer HealthCare, Heidelberg Engineering	No	No	No	Yes BVA, DOG, RG	No	University Hospital Bonn, Germany	No
Holz, Prof. Dr. med. Frank G	Yes Acucela, Allergan, Bayer, Novartis, Genentech/Roche, Heidelberg Engineering	Yes Allergan, Bayer, Novartis, Genentech/Roche, Heidelberg Engineering	Yes Acucela, Allergan, Bayer, Novartis, Genentech/ Roche, Heidelberg Engineering, Optos, Zeiss	No	No	No	Yes DOG, BVA, Euretina	No	University Hospital Bonn, Germany	No
Maier, Prof. Dr. Mathias	No	Yes Lecture fees from Allergan, Bayer, Novartis, Heidelberg Engineering, Zeiss	Yes Novartis, Bayer	No	No	No	Yes BVA, DOG, RG	No	Ophthalmology Department and Outpatient Clinic, Klinikum rechts der Isar, Technical University of Munich, Germany	No
Pauleikhoff, Prof. Dr. med. Daniel	Yes Novartis, Bayer, Roche	Yes Novartis, Bayer, Roche	No	No	No	No	Yes DOG, BVA, RG	No	Independent	No

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