REVIEW ARTICLE

The Treatment of Wet Age-Related Macular Degeneration

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SUMMARY

Background: Age-related macular degeneration (AMD) is a progressive disease affecting the macula, the area of the retina that has the highest visual acuity. It can progress to geographic atrophy or choroidal neovascularization.

Method: Selective literature review.

Results: The authors discuss the results of therapeutic trials and the treatment recommendations of the ophthalmological societies. Mechanism-targeted treatments and improved modes of administration offer the potential for improved therapy.

Conclusions: With the advent of the antivascular endothelial growth factor (anti-VEGF) therapy, the prognosis of choroidal neovascularization has changed dramatically. Visual acuity can actually be improved, but, in most cases, the improvement can only be sustained with repeated intravitreal injections.

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Key words: macular degeneration, age-related macular degeneration, off-label treatment, treatment, monoclonal antibodies

The use of vascular endothelial growth factor (VEGF) inhibitors to treat age-related macular degeneration has been widely covered in the press and has generated much public discussion, in which highly subjective points of view are often expressed (1). This article is a selective review of the literature based on a PubMed search for the terms "age-related macular degeneration" and "therapy" as well as on the current health policy debate over this matter in Germany (e1).

Age-related macular degeneration is the most common cause of blindness in the elderly (2, e2). Although only a minority of patients with late age-related macular degeneration (AMD) lose enough visual acuity to qualify as legally blind (see *table 1*) (e3), most patients with advanced AMD have only poor residual vision and thus meet the definition of "severe visual impairment" currently in use in Germany (*table 1*). Exudative, or "wet," AMD is a late form of AMD (as distinguished from atrophic, so-called dry, AMD) and is responsible for 60% to 80% of all cases of blindness due to AMD. The prevalence of advanced AMD is estimated at 1.47% in the United States population (e4). An extrapolation to Europe yields a prevalence figure of 3.5% among persons over age 65 (3).

Pathogenesis

The cells of the retinal pigment epithelium (RPE) play a central role in the pathogenesis of age-related macular degeneration. They are responsible for the generation and maintenance of the extracellular matrix, the photoreceptor matrix, and the membrane of Bruch, as well as for ion and fluid transport between the photoreceptors and the choroid membrane and for phagocytosis in the external segments of the photoreceptors. If these cells do not function properly, lipids and proteins accumulate in the area of Bruch's membrane, and Drusen are formed (4, 5).

The wet type of macular degeneration arises in only about 10% of all patients, among whom the main cause of blindness is neovascularization. Angiography permits various subtypes to be distinguished from one another; these subtypes are histologically characterized by vascular growth above or below Bruch's membrane. The terms that were originally introduced to distinguish them—"subfoveal," "subfoveolar," "juxtafoveal," and "extrafoveal"—are not now used in any uniform way. It is best, therefore, to draw only a single distinction between subfoveal, i.e., choroidal, neovascularization (CNV),

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which has not yet reached the avascular zone of the fovea, on the one hand and non-subfoveal membranes on the other (6, 7). Choroidal anastomoses and pigment epithelium detachments are special, distinguishable subtypes (e5).

Treatment

Dry age-related macular degeneration is mainly treated with medical dietary supplementation (e7), although a number of surgical options are currently under investigation (e6). In contrast, the treatment options for the wet form of the condition have been markedly expanded in recent years by the introduction of anti-VEGF medications. This type of anti-angiogenic therapy is the first effective treatment offering not merely a slowing of the natural progression of the disease, but actually an improvement of visual acuity (6, e8).

Thermal photocoagulation

Thermal coagulation with the argon ("hot") laser is beneficial for patients with an exclusively extrafoveal membrane, i.e., one lying outside the avascular zone of the fovea (e9); this is the case in only about 5% of all patients. Thermal coagulation produces a scar that goes through all layers of the retina and that manifests itself clinically as a visual field defect. Therefore, the use of this treatment is restricted to the extrafoveal area. It is associated with a rather high recurrence rate (almost 50%).

Photodynamic therapy

Photodynamic therapy (PDT) with verteporfin has been tested in a number of prospective studies for the treatment of various subtypes of exudative, subfoveal AMD (8, e10). In 2000, the United States Food and Drug Administration (FDA) approved PDT with verteporfin for the treatment of predominantly classic, subfoveal choroidal neovascularization. Since then, many international studies have followed, investigating the potential indications of the technique in subtypes of wet age-related macular degeneration, in pathological myopia, and (in smaller studies) in choroidal neovascularization of other causes (e11, e12). Nonetheless, statutory health insurance in Germany no longer reimburses this form of treatment for occult membranes (e12). The latest recommendations of the German Ophthalmological Society classify PDT as a second-line treatment after the anti-VEGF therapies. Nonetheless, in certain cases, PDT can still play a useful role in combination therapy, in addition to growth factor inhibitors.

Treatment with VEGF inhibitors

The idea of a growth factor for blood vessels was first proposed by Michelson in 1948. Folkman and his research team, in the early 1970's, were able to show that tumor growth is closely related to the growth of tumor vessels, which, in turn, depends on the expression of special growth factors (9). Overexpression of vascular endothelial growth factor (VEGF) is considered to be the cause of choroidal neovascularization (10, e13). This

TABLE 1

Definitions in age-related macular degeneration

Legal blindness	Visual acuity ≤ 0.02 in the better eye
Severe visual impairment	Visual acuity ≤ 0.05 in the better eye
Wet (= exudative) macular degeneration	Choroidal neovascularization (CNV) above or below the pigment epithelial cells
Junius-Kuhnt maculopathy	Burned-out, fibrotic scarring due to prior wet macular degeneration
CNV	Choroidal neovascularization
Pigment epithelium detachment	Serous detachment of the pigment epithelium, usually due to choroidal neovascularization beneath it
Dry (= atrophic) macular degeneration	A disturbance of the pigment epithelium cells causes their demise, with secondary loss of the choroid

growth factor selectively influences the growth of endothelial cells; in particular, it is responsible for vascular leakage, i.e., the pathological egress of fluid from the interior of blood vessels (e14).

The treatment of wet macular degeneration with anti-VEGF substances can be considered a milestone. Now, for the first time, an opportunity exists to treat neovascularization more directly and to inhibit it selectively.

Three medications of this type are currently in use:

- pegaptanib,
- ranibizumab, and
- bevacizumab.

Pegaptanib

Pegaptanib is an aptamer, i.e., a low-molecular-weight receptor molecule that captures bioactive VEGF before it has a chance to exert an effect on the cell. It inhibits only the VEGF 165 isoform, and none of the others. The effectiveness of treatment with pegaptanib has been demonstrated in phase III clinical trials, e.g., the VISION study (11, 12).

If pegaptanib is discontinued after one year of treatment, further growth of CNV is frequently observed. Continuous treatment for two years is significantly more effective, particularly in patients with early lesions of exudative AMD (e15, e16).

The positive results of prospective, randomized phase III trials led the FDA to approve pegaptanib on 17 December 2004 for the treatment of various subtypes of neovascular age-related macular degeneration (e15). The European Medicines Agency (EMA) approved pegaptanib for use in the European Union on 31 January 2006, and the drug has been available in Germany since May 2006. Because the study findings to date have shown that pegaptanib can do no better than to stabilize (rather than improve) the patient's visual acuity, the German Ophthalmological Society recommends it only as a second-line treatment. It cannot yet be judged whether

TABLE 2

Summary of visual acuity findings for approved treatments of choroidal neovascularization (6)

Treatment (study)	Length of treatment (months)	Mean change (letters on the ETDRS chart; 5 letters constitute one line on the visual acuity chart)			Difference of more than 15 letters
		Treated	Control	Difference	
Laser (MPS) (e9)	24	−15.0	−22.0	7.0	20%
Verteporfin (TAP) (e10)	12	−11.0	−17.5	6.5	15%
Verteporfin (TAP) (e35)	24	−13.5	−19.5	6.0	15%
Verteporfin (VIP) (e11)	24	−19.0	−25.5	6.5	12%
Pegaptanib (VISION) (e16, e36)	12	−8.0	−15.0	7.0	15%
Ranibizumab (MARINA) (13)	12	+6.8	−10.4	17.2	33%
Ranibizumab (ANCHOR) (12)	12	+11.3	−9.5 (PDT)	20.9	37%

The laser coagulation studies are included for comparison with pharmacotherapy.

MPS, Macular Photocoagulation Study; TAP, Treatment of Age-Related Macular Degeneration With Photodynamic Therapy; VIP, Verteporfin in Photodynamic Therapy; VISION, VEGF Inhibition Study in Ocular Neovascularization in Age-Related Macular Degeneration; ANCHOR, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA, Minimally Classic / Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration

better results might be obtained by combining pegaptanib with PDT or with other VEGF inhibitors (e17).

Ranibizumab

Ranibizumab is a humanized monoclonal antibody fragment (Fab fragment; antigen-binding fragment) that binds all isoforms of VEGF-A. It inhibits the growth of CNV membranes, as well as CNV-induced macular edema. The studies that have been published to date show a better therapeutic effect for ranibizumab than for the aptamer pegaptanib.

12- and 24-month results are not yet available from two phase III trials (13, 14) in which ranibizumab was injected into the vitreous body at four-week intervals.

In the MARINA study, in which ranibizumab was used to treat minimal classic or occult CNV in 716 patients, more than 90% of the treated patients had a significantly improved visual acuity at both 12 and 24 months after the start of treatment (14).

Similarly, in the ANCHOR study, in which ranibizumab was used to treat 423 patients with predominantly classic CNV, about 95% of the treated patients had lost fewer than three lines of visual acuity in 12 months (three lines = significant loss of acuity), compared to 64% of the patients who had received PDT with verteporfin (13).

Ranibizumab is the first treatment for neovascular AMD with an approved medication (approval in January 2007) that can improve the patient's visual acuity. In the United States, monthly administration of ranibizumab is recommended; in contrast, the physicians' information sheet (Summary of Product Characteristics [SPC]) issued

after the approval of the drug in Europe recommends an initial loading with three injections, followed by individually tailored maintenance therapy based on the course of the patient's visual acuity (Novartis information for physicians) (table 2).

Less common applications of this drug are under study in three clinical trials that are currently in progress (PIER, PrONTO, and SAILOR). The preliminary findings of the PrONTO trial suggest that less frequent injections can produce similar results to those obtained in the published phase III studies (e18), yet preliminary findings of the PIER trial suggest that lengthening the interval between injections leads to a worse result (e19). In view of its proven ability to improve visual acuity, ranibizumab has been recommended as a treatment for neovascular macular degeneration both by the scientific ophthalmological societies and by the German Association of Ophthalmologists.

Bevacizumab

Bevacizumab is a humanized complete antibody directed against VEGF-A and is closely related to the antibody fragment ranibizumab (e20). It has now been shown that the larger molecule bevacizumab completely penetrates the retina and choroid membrane after intravitreal application (15, e21).

Bevacizumab is recommended, in combination with cisplatin and paclitaxel, as the first line of therapy for patients with metastatic colorectal carcinoma and in subgroups of patients with advanced, metastatic carcinoma of the lung. In 2007, it was approved in Europe for the treatment of renal and breast cancer as well.

TABLE 3

Recommendations of the German Ophthalmological Society, the German Retinological Society, and the German Association of Ophthalmologists for treatment with VEGF antagonists (6)

Diagnosis of exudative AMD	Fluorescein angiography	Gold standard for establishing the indication and for monitoring progression
	Optical coherence tomography (OCT)	Supplementary treatment, not sufficient by itself
Frequency and endpoint of treatment	Retreatment	Recommended loading phase of three injections at four-week intervals, then retreatment in case of disease progression: – decline in visual acuity – new macular hemorrhages – increasing macular edema
	Treatment endpoint	– if the visual acuity is stable and no new hemorrhages or macular edema arise – if angiography reveals no progression – termination of treatment if visual acuity < 0.05* ¹

*¹ Termination of treatment should certainly be considered if new hemorrhages arise and further loss of visual acuity or deterioration of the visual field is feared

The use of bevacizumab for the treatment of intra-ocular retinal and choroidal neovascularization has been studied to date in a wide variety of clinical trials, most of them without a control group (16, e22, e23). The positive findings are comparable overall with the improvement of visual acuity achieved in the MARINA and ANCHOR trials after a few months' treatment with ranibizumab. As far as can be judged from the published data, there is no evidence for any major difference in the effect of bevacizumab against various angiographically distinguishable membrane subtypes (e24). Even though meta-analyses have yielded a judgment that bevacizumab is, in all probability, not inferior to ranibizumab, any potential difference cannot be definitively assessed till data are available from a prospective, randomized comparative trial (17).

The intravitreal application of bevacizumab lies outside the indications for which this drug has been approved and thus constitutes off-label use (table 3).

The safety of treatment with anti-VEGF medications

The reported side effects of anti-VEGF medications given intravenously at high doses for oncological indications include medically manageable hypertension (hypertensive crisis, 1.6%) and thromboembolism, the risk of which increases with age (up to 4.4%).

Neovascular, age-related macular degeneration is, among other things, a sign of vascular dysregulation. The combined risk of heart attack or stroke after intravitreal administration in the first year of the ANCHOR and MARINA trials was no different in the control groups and in the ranibizumab 0.3 mg groups (1.3% versus 1.6%). As in other studies, no difference was found at two years when higher doses were used (e25).

Yet, in February 2007, the FDA observed critically that the rate of stroke in both dose arms of the SAILOR study was lower than that in the approval studies, but no corresponding mention of an elevated risk had been made in the drug information for physicians. This judgment resulted from a comparison of the incidence of stroke in the age group in which AMD typically appears with that in the treatment arms of the ranibizumab approval studies (e26).

There are no data from controlled studies with respect to the off-label intravitreal injection of bevacizumab. The results of 7113 injections in 5228 patients were analyzed on the basis of a questionnaire over the Internet: the rate of hypertension, transient ischemic attacks, and cerebrovascular accidents was no higher than 0.21% (18). There is no evidence to date suggesting that the systemic complications are any more common than those following the intravitreal application of ranibizumab.

It remains fundamentally true, however, that the systemic concentration of the drug might cause relevant changes in tissues outside its immediate area of application (e27).

Ocular side effects of injection, including corneal abrasion, damage to the lens, endophthalmitis, retinal detachment, or vascular occlusion, have been described for all of the medications that are in use, in roughly equal frequencies (19).

A specific complication (tearing of the pigment epithelium) that can permanently impair visual acuity has been observed after bevacizumab injections for the treatment of a specific subtype of wet macular degeneration (extensive pigment epithelium detachment) (19). Initial reports, however, reveal a comparable frequency of this complication after treatment with ranibizumab (20). In patients with preexisting pigment epithelium

detachment, the treating physician should assess the risks and benefits carefully.

Further information on cost-effectiveness and off-label use can be found online (*e-box*).

The duration of treatment

At first, three injections are recommended. If the initial effect of treatment is positive, further treatment should be given after the third injection in case the clinical examination and follow-up fluorescein angiography reveal disease progression (worsening of visual acuity, new hemorrhage[s] in the macula, increase or reactivation of macular edema and/or CNV). Even in the absence of relevant study data concerning the optimal duration of intravitreal injection therapy with any of the currently used anti-VEGF drugs, further treatment would seem not to be indicated if the visual acuity sinks below 0.05, or if extensive subretinal fibrosis or atrophy develops. Further treatment may be beneficial, however, when fresh hemorrhages have occurred at the periphery of the membranes.

In accordance with the guiding principles of treatment described above, the treatment should be terminated only if the above criteria for continuing therapy and for disease progression are not met after a temporary pause in the treatment, or if the clinical findings worsen substantially despite an uploading dose. Termination of treatment should also be considered if further treatment seems unlikely to stave off a loss of visual acuity, i.e., if functional and morphological end-stage disease is already present (6).

Alternative treatments

Combination therapy

The intravitreal administration of steroids alone can no longer be recommended, in view of the results of VEGF inhibitor treatment that are described here. Nonetheless, combined treatment appears to be a promising approach.

Case series and randomized studies have shown that PDT combined with intravitreal triamcinolone can stabilize visual acuity and prolong the interval between treatments (e30). Similarly, synergistic effects of bevacizumab and PDT have been described in a number of studies (8, e31). The FOCUS trial studied the combination of ranibizumab with PDT; according to the initial results, however, combined therapy was no better at improving visual acuity than ranibizumab alone, though it did seem to lower the frequency of injections.

It is clear that the potential benefit of triple combinations, such as a combination of PDT, triamcinolone, and pegaptanib (e31) or of PDT, intravitreal dexamethasone, and intraocular bevacizumab (e32), can only be definitively assessed with long-term studies. The results reported to date have not been confirmed in controlled trials.

Surgery

Having seen the current possibilities for treatment with anti-VEGF drugs, one may well ask whether surgical methods have any role left to play. A comparison of the

results of the Submacular Surgery Trial (SST) (21), or of rotation (e33) or patch translocation (i.e., transplantation of the choroid membrane and the pigment epithelium) (e6, e34), with the latest publications on pharmacotherapy indeed makes clear that medical treatment is vastly superior with respect to the improvement of visual acuity. Massive subretinal hemorrhage is a medically untreatable entity that will remain in the domain of surgical treatment.

Other types of pharmacotherapy

The number of angiostatic substances being tested in oncology today that might also be useful in the eye is already too large to be encompassed in a brief overview. The *e-table* lists a selection of candidate substances that have already been tested in experimental models of ocular neovascularization or in clinical trials.

The potential for a substance that has been tested in the laboratory to be developed into a medical treatment is a function not only of its effectiveness at inhibiting angiogenesis in vitro and in vivo, but also of the degree to which it influences physiological mechanisms. It has been shown that VEGF and its receptors are expressed in the normal retina as well, and there is still no answer to the question whether inhibiting VEGF or other factors that are normally present might harm the functioning of neurons or other cells over the long term (22). The value of these novel types of therapy will thus depend, not just on their systemic risk profile, but also to a large extent on the changes they induce in the local microcosm of the retina.

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Conflict of Interest Statement

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Key messages

- Anti-VEGF therapies are a milestone in the treatment of neovascular age-related macular degeneration, as they are the first form of treatment that offers a chance of improved visual acuity.
- Currently, repeated injections into the vitreous body are still necessary. These must be performed under sterile operating conditions, and their indication must be established according to criteria of disease progression and the effectiveness of treatment.
- Ranibizumab is generally the medication of choice. Patients should also be informed about the option of treatment with bevacizumab.
- Initial studies have now revealed that anti-VEGF treatment for age-related macular degeneration also has its limitations (23). For patients that do not respond to anti-VEGF treatment, new approaches must be evaluated for the inhibition of neovascularization through other metabolic pathways.
- Large submacular hemorrhages can only be treated surgically at present.

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REVIEW ARTICLE

The Treatment of Wet Age-Related Macular Degeneration

Antonia M. Joussen, Norbert Bornfeld

E-BOX

Cost-effectiveness and the off-label debate

New treatments such as ranibizumab (Lucentis) or pegaptanib (Macugen) have given rise to a new problem in economics and thus also in health policy. Intraocular injections for the pharmacotherapy of age-related macular degeneration have not yet been included in the catalog of reimbursed medical services in Germany (Einheitlicher Bewertungsmaßstab, EBM).

The cost of a single dose of ranibizumab is currently about €1296. Bevacizumab is considerably cheaper: the single dose needed for intraocular use is about €50. Nonetheless, ranibizumab is still cost-effective, according to generally accepted criteria.

The intraocular use of bevacizumab is an off-label treatment. This medication is currently approved only for the systemic treatment of colon carcinoma. Even though more than 10 000 observations of the intraocular use of bevacizumab in human patients have now been documented, there have been no trials meeting the requirements for phase III approval studies as defined by the German Law on Pharmaceuticals (Arzneimittelgesetz, AMG).

In Germany, the Federal Social Court (Bundessozialgericht, BSG) and the Federal Constitutional Court (Bundesverfassungsgericht, BVerfG) have established that medications may be used off-label if certain criteria are met: serious illness, lack of an alternative, and reliable evidence of effectiveness. Since the introduction of ranibizumab, however, the requirement that there be no alternative is no longer fulfilled in the case of bevacizumab. "Reliable evidence of effectiveness" can be gained outside the approval process from reliable, scientifically based, and testable results of treatment, as well as from a consensus among users.

A number of large randomized and controlled studies in which the effectiveness of bevacizumab will be directly compared with that of ranibizumab are currently in the planning or recruitment phase, including the CATT study in the USA (e28) and the VIBERA study in Germany. The VIBERA study will investigate not just the non-inferiority of bevacizumab, but also its theoretically possible advantages, e.g., a longer half-life.

The current debate in the ophthalmological setting about the question of cost in the treatment of age-related macular degeneration is important in view of the need for cost-effectiveness in the health care system as a whole. A calculation of the cost-effectiveness of treatments expressed in quality-adjusted life years (QALYs) has recently been published. One result of this calculation, for example, is the following: ranibizumab, which is currently 50 times more expensive than bevacizumab, would have to have a 2.5 times better result on visual acuity in order to be considered equally cost-effective (e29).

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E-TABLE

Possible alternative medications for therapeutic and diagnostic use

Anecortave acetate (e38–e42)	<ul style="list-style-type: none"> • anti-angiogenic steroid • posterior juxtascleral injection • AMD: anecortave acetate (15 mg) is superior to placebo treatment (statistically significant finding) for the stabilization of visual acuity • under investigation for RAP lesions and idiopathic parafoveal telangiectases
Dexamethasone implant (e43)	<ul style="list-style-type: none"> • intravitreal slow-release system for patients with persistent macular edema • improved visual acuity in patients with dexamethasone (700 µg [35%] or 350 µg [24%] higher than in control patients [13%]) • increased intraocular pressure in treated patients
VEGF trap (e44)	<ul style="list-style-type: none"> • recombinant soluble VEGF receptor protein • binding domains of VEGF receptor 1 (VEGF-A and PDGF) and receptor 2 (VEGF-A, VEGF-B, and VEGF-C) are linked to the Fc fragment of immunoglobulin G • phase II study in 25 patients with neovascular age-related macular degeneration (intravenous therapy) • 1.0 mg/kg is the maximum tolerated dose • dose-dependent reduction of retinal thickness (measured by OCT) • a pilot study shows reduction of CNV size measured by angiography
siRNA (e45)	<ul style="list-style-type: none"> • small interfering RNA (siRNA) against vascular endothelial growth factor receptor 1 (VEGFR-1) mRNA • inhibits neovascularization in a murine model of ischemic retinopathy
PEDF (pigment epithelium derived factor) (e46)	<ul style="list-style-type: none"> • PEDF regulates the normal growth of blood vessels • an open-label, non-comparative trial of the intravitreal injection of a modified adenoviral PEDF-expressing vector (AdPEDF.11): 28 patients with choroidal neovascularization due to AMD • mild intraocular inflammation and increased intraocular pressure • 6 months after injection, 50% to 71% of patients had no significant loss of visual acuity
RTP801 Hypoxia inducible factor (HIF)-1 responsive gene (e47)	<ul style="list-style-type: none"> • in a murine model of the retinopathy of prematurity, findings are less severe in mice that are deficient in HIF-1α • an antisense molecule for RTP801 is currently under study
Polyamine (e48–e49)	<ul style="list-style-type: none"> • new polyamines: periocular, intravitreal injection or transscleral iontophoresis • suppression and regression of laser-induced CNV membranes in various murine models

Substances are listed only if preclinical or clinical data were available on them as of August 2007;
The literature is listed under e1–e12