NO EFFICACIOUS TREATMENT FOR AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

Purpose: The purpose of this paper is to explain that many trials have been done unsuccessfully to improve age-related macular degeneration.
Methods: Different trials that have been done to improve this degeneration and that have been published in a peer reviewed journal are discussed.
Results: There is not yet a preventive therapy that has a significant impact on blindness due to age-related maculopathy. There is no therapy for geographic atrophy. There are limited forms of therapy with the objective of destroying new vessels arising in the choroid and of limiting the visual loss.
Conclusion: There is a need for more efforts to find ways that influence the survival of the complex photoreceptor - retinal pigment epithelium - Bruch's membrane in the aging population.

RESUMÉ

But: Comment expliquer qu'il n' y ait pas de traitement satisfaisant pour la dégénérescence maculaire liée à l'âge.
Méthode: L' auteur a résumé plusieurs modes de traitement qui ont été proposés et publiés dans la littérature.
Résultats: Il n' y a pas de traitement préventif dans les stades précoces. Il n' y a pas de traitement satisfaisant pour les formes non-exudatives. Il n' y a que peu de possibilités afin de détruire des néovaisseaux sous-rétiniens centraux et à préserver la vision centrale.
Conclusion: Il nous faut faire plus d'efforts afin de trouver un moyen qui garantira une survie plus longue au complexe photorécepteur - épithélium pigmentaire rétinien - membrane de Bruch chez les personnes âgées.

SAMENVATTING

Doel: Aandacht vragen voor het gegeven dat er geen goede behandeling is voor leeftijdsgebonden degeneratie van de macula (AMD).
Werkwijze: Enkele behandelingsmogelijkheden (het opsporen van risicofactoren, laser-, bestralingstherapie, medicatie,...) die de laatste jaren aangeprezen werden in de literatuur worden besproken.
Resultaten: Er is geen preventieve therapie die slechtzien ten gevolge van AMD voorkomt; er is geen therapie voor de droge vorm van AMD. Er zijn slechts beperkte behandelingsmogelijkheden voor de neovasculaire vorm van AMD.
Besluit: Er moet meer werk gemaakt worden van het zoeken naar een middel dat een langere levensduur waarborgt van het geheel fotoreceptor - retinaal pigment epitheel - membraan van Bruch.

KEY WORDS

Age-related macular degeneration - treatment

MOTS CLÉS

Dégénérescence maculaire liée à l'âge - traitement

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Age-related macular degeneration has become a major cause of visual loss in patients older than 60 years. It is caused by basic changes related to the aging process that occur at the level of the retinal pigment epithelium (RPE), Bruch's membrane, and possibly the choriocapillaris (12, 22, 23, 67, 70). These changes lead to the characteristic manifestations of age-related macular degeneration. The purpose of this paper is to survey the many trials done unsuccessfully to improve macular degeneration. Therefore, more efforts should be carried out to do further research in this severe problem.

I. RISK FACTORS: GOAL OF RESEARCH

I.1 One of the initiatives to unravel the mystery of degenerative disorders of the macula in patients more than 50 years of age was to compose an international epidemiological study group in order to study the natural history and risk factors, to set up a definition and to develop a core grading system. The international ARM epidemiological study group defined *age-related maculopathy* (ARM) as: ″a degenerative disorder of the central area of the retina (the macula) often associated with visual impairment, which is more frequent after 65 years of age″ (56). ARM is defined primarily on the basis of morphological changes seen on color fundus transparencies and characterized by any of the following primary signs: soft drusen (46), areas of increased pigment or hyperpigmentation associated with drusen, areas of depigmentation or hypopigmentation associated with drusen. Hard drusen do not of themselves characterize the disorder (56). Visual acuity is not a criterion for the presence or absence of ARM. *Age-related macular degeneration* (AMD) is a term reserved for the late stages of ARM. Geographic atrophy of the RPE and secondary choroidal atrophy is one end result in eyes with macular drusen. The international study group called this stage ″dry AMD″. ″Wet AMD″, also called ''neovascular'' AMD, is another end result in eyes with macular drusen and is characterized by any of the following: detachment of the retinal pigment epithelium, subretinal or sub-RPE neovascular membrane(s), subretinal hemorrhage, subretinal or preretinal scarring and lipid exudation.

I.2 It seems likely that genetic predisposition is a strong risk factor apart from advanced age. In a number of cases AMD is familial and inherited as an autosomal dominant trait. It is more frequent in women. There is a protective effect of ocular pigmentation. There is reason to believe that environmental influences are important to a subgroup of patients with AMD who have inherited one particular combination of disease susceptibility genes. An important goal of research is to identify these factors, evaluate their significance and develop practical methods of counteracting them (68). Possible risk factors are: solar radiation, smoking, coronary artery disease, systemic hypertension, iris color, a cardiovascular risk factor profile, lens opacities or history of cataract surgery, hyperopia, low intake of antioxidants and other micronutrients, anticoagulants and non specific exposure to chemicals (6, 53, 68). Smoking is the best characterized risk factor for late ARM (14).

I.3 Drusen larger than 63 μm (half the width of a large vein at the disc) and focal hyperpigmentation in the central macula, a slower glare recovery time (10 seconds of exposure to an ordinary pen light) are significant independent age-adjusted predictors for development of a neovascular membrane in the fellow eye of patients with neovascular AMD in one eye (32, 45).

II. PROPHYLAXIS

II.1 Spinach for macular drusen?

There is increasing speculation that dietary factors, particularly antioxidants, may prevent or impede the progression of AMD. Increasing intake of food that is rich in carotenoids may reduce the risk of developing advanced AMD. Dark green leafy vegetables, such as spinach, are rich in lutein and zeaxanthin, which are the dominant pigments in the macula. These yellow pigments, lutein and zeaxanthin, are selectively accumulated in the retina from plas-

ma and can filter out visible blue light, which theoretically can cause photic damage. Ultraviolet light is filtered by the cornea and lens in the anterior aspect of the eye, but visible blue light reaches the retina. Therefore, lutein and zeaxanthin might serve to protect the retina from photic damage or other oxidative insults. Further studies are needed to examine the relationship between increasing the consumption of food rich in dark green, leafy vegetables and in other nutrients and the risk of developing AMD (4,52).

II.2 Light filtration

Light filtration should be investigated in the hope of decelerating progressive, atrophic degeneration and perhaps of reducing the conversion rate from non-exudative to exudative disease (66).

Van der Hoeve found in 1918 a correlation between opacities of the lens and the protection against AMD. This correlation is not well understood. The human lens is the major factor that protects the retina from the hazardous effects of short-wavelength radiation, which penetrates the cornea (68). Developers of intraocular lens material do their best to use material that blocks ultraviolet radiation (65). It was sometimes feared that after cataract extraction with implantation of an intraocular lens, the increased transmission of light might accelerate the development of neovascular AMD. So far, there is no confirmation that AMD is caused by an increase in ultra-violet or blue light after cataract extraction with lens implantation (61).

II.3 Laser for macular drusen

The past few years have seen a series of attempts to delay the onset of macular degeneration by laser treatment of drusen following the observation that their number and size can be reduced with laser therapy. However, the initial enthusiasm has waned somewhat since early results showed that not only some patients are not helped by this treatment but that some can actually be made worse either directly or because of secondary complications. For now it appears that this treatment is unlikely to become the standard approach for prophylaxis of macular degeneration (1, 37, 47, 54, 55).

III TREATMENT

III.1 Laser for choroidal neovascular membranes (CNV)

Laser (light amplification by stimulated emission of radiation) is a palliative approach. Its application eliminates the neovascular membrane to limit the destructive effects. Due to heat conduction, the entire outer retina overlying and surrounding the lesions, as well as neighboring RPE and choroid, usually are irreversibly damaged. Argon lasers have been used for retinal photocoagulation since their introduction by L'Esperance in 1968.

Good results with argon laser in the treatment of neovascular AMD have been published many years ago (60). The Macular Photocoagulation Study (MPS) (18, 31) is the largest controlled prospective randomized clinical trial addressing the issue of laser treatment for CNV in AMD and therefore is justly accepted as the gold standard in the management of these difficult cases. Those cases that do not meet its inclusion criteria do have a poor prognosis. These guidelines include strict definition of the clinical and fluorescein angiographic appearence, the size of the lesion and the status of the visual function. The MPS-treatment guidelines and published results pertain to patients who have a CNV that is well demarcated on fluorescein angiography (classic CNV). These guidelines presume that successful treatment of the neovascular process demands complete obliteration of the lesion. The MPS has demonstrated the efficacy of laser photocoagulation in the treatment of extrafoveal, juxtafoveal, and selected cases of subfoveal CNV in AMD to prevent or slow down loss of visual acuity. However, these membranes often persist after laser treatment. Laser treatment of subfoveal CNV usually results in an absolute central scotoma and a permanent, sudden decrease in visual acuity. However it was also shown that untreated cases with subfoveal CNV fare more poorly vision wise that treated cases. Current imaging and laser treatment modalities available for neovascular

AMD are less than ideal. Only a small proportion of those with visual loss in clinical practice (about 10%) will be eligible for laser treatment and even in these patients it has limited success. Despite promising expectations, it is now increasingly evident that laser treatment will not significantly reduce the severe visual loss experienced by most patients with this macular disease. ±50 % of those treated will have recurrent CNV in the years following treatment. The vast majority of the patients have occult CNV or/and CNV that its too large. That is why it is necessary to search for better ways to visualize these neovascular membranes and for better modalities to treat them. Indocyanine green angiography which permits a better visualisation of subretinal neovascularisation has become an essential tool in the diagnosis of AMD and in assessing the treatment strategy (8).

III.2 Photodynamic therapy for CNV

Photodynamic therapy (PDT) combines the noninvasive potential of the laser light with the nonthermal approach of a localized chemo-toxic reaction. A photoactivable drug is administered intravenously. The sensitizer is distributed throughout the organism with preferential accumulation in the pathologic structure (the neovascular membrane of the choroid in case of AMD). Exposure to light induces a photochemical process based on the generation of singlet oxygen, free radicals and other cytotoxic molecules (50).
Highly selective occlusion of neovascular channels and maintenance of overlying photoreceptors is required for adequate treatment of CNV and to obtain results superior to those achieved by thermal photocoagulation. This therapy will probably be of no proven benefit because PDT is a symptomatic treatment of CNV, which does not eliminate the angiographic stimulus in neovascular AMD. PDT itself may induce neovascular growth by impairment of choriocapillary perfusion and by causing a localized inflammatory reaction with cytokine release promoting leakage and recanalization.
There are in America two ongoing trials for the treatment of AMD: the Photodynamic Therapy (TAP investigation) and the Verteporfin in Photodynamic Therapy (VIP) trial under the supervision of Dr. Bressler. The TAP trial is constructed to demonstrate whether PDT, in patients who have subfoveal neovascularization with evidence of classic neovascularization in AMD will reduce the risk of vision loss (5, 59). The VIP trial is constructed for patients with recent lesions that were not eligible for TAP, predominantly occult CNV without classic CNV.
Data were published on the effects of a single treatment of PDT with verteporfin (''verteporfin therapy'') on patients with subfoveal CNV secondary to AMD (36). It was concluded that this therapy can lead to cessation of fluorescein leakage from CNV for 1 to 4 weeks, with stabilization or improvement of vision for 12 weeks. Also data were published on the effects of retreatments with verteporfin for CNV in AMD that demonstrated fluorescein leakage after at least 1 course of PDT (51). It was concluded that multiple applications of PDT with verteporfin achieve repititive, short-term cessation of fluorescein leakage from CNV secondary to AMD, without loss of visual acuity. Retreatments may achieve progressive cessation of leakage and prevent further growth of CNV and subsequent visual loss. The long-term prognosis of CNV secondary to AMD treated with repeated courses of PDT is being evaluated in a phase III trial.
The results of a trial with the photoactivable drug $SnET_2$ were also reported (57).

III.3 Transpupillary Thermotherapy (TTT)

TTT is a technique in which heat is delivered slowly to the choroid and retinal pigment epithelium through the pupil using a modified diode laser. It has been reported to be effective for choroidal melanoma. Reichel et al published a pilot study to evaluate the efficacy of TTT for the treatment of occult subfoveal CNV in patients with AMD. No deleterious side effects were reported. Randomized, prospective studies using larger numbers of patients will ultimately determine the role of TTT in the treatment of occult CNV (25, 43).

III.4 Radiation therapy for CNV

Radiation therapy is known to have the potential to destroy vascularized tissue and prevent

neovascularization. Radiobiologists believe it is possible to use a dose of radiation, which is high enough to induce regression of CNV but low enough to spare the normal retina and choroid. Randomized controlled clinical trials are necessary to search for this proper radiation therapy method, the optimal radiation dose, the appropriate dose fractionation and the target volume of tissue that should be irradiated. Some ophthalmologists consider these trials as too expensive to do and therefore do not advocate radiation as a modality to treat AMD (48).
Chakravarty et al were the first to report a pilot study about the treatment of age-related subfoveal neovascular membranes by teletherapy (9). That study was designed to determine whether low dose radiation to the macular region could influence the natural course of age-related subfoveal neovascularization. Since this report, the results of a number of case series of eyes with CNV treated with radiation therapy have appeared in the literature. The reported results are controversial: some retrospective studies in the evolution of the visual acuity after radiation therapy did not show a greater beneficial effect on the evolution of CNV than the natural course and severe late complications were reported after radiation therapy for wet AMD (13, 33, 35, 41, 42, 63).

III.5 Drug therapy

III.5.a Improving the choroidal blood flow?

Recent studies indicate that the blood flow in the choroid is impaired in patients with AMD. Pentoxifylline is a synthetic xanthine derivate that has the ability to increase the ocular blood flow due to its direct vasodilator action and due to the improved deformability of erythrocytes and leukocytes. A double-blind, randomized, parallel group study indicated that a 3 month treatment with oral pentoxifylline, 400 mg 3 times a day, increases choroidal blood flow in patients with AMD. Long-term clinical outcome trials are necessary to evaluate the therapeutic value of the drug (28).

III.5.b Drug therapy for CNV

Choroidal new vessels, often clinically unsuspected, are commonly found on histological examination of post-mortem eyes suffering from ARM. The early new vessels grow initially in the cleavage plane created by a diffuse layer of debris external to the basement membrane of the RPE. It is not well understood why some of these new vessels start to grow. The confluence of soft drusen opens the forementioned cleavage plane. The progress of active choroidal neovascularization is therefore influenced by the nature and quantity of the debris present. Treatment modalities should attempt to confine the activity of these neovascular membranes as much as possible.
Pharmacological antiangiogenic intervention would permit to avoid or minimize laser-induced damage and to treat vessels that cannot be well imaged. It might also be a prophylactic agent for this disease.

Interferon - 2a
Interferon-2a inhibits vascular endothelial cell proliferation and migration. In humans, interferon is effective as an antiangiogenic agent for life-threatening hemangiomas in infants and for Kaposi sarcoma in patients with the acquired immunodeficiency syndrome. A randomized, placebo-controlled, parallel, multicenter, double-blind trial could not show a benefit from interferon-2a as a treatment for choroidal neovascularization secondary to ARM. Moreover, it is expensive and fraught with many undesirable side effects (i.e. interferon associated retinopathy and the possibility of a poorer visual outcome) (7, 40).

Thalidomide
Thalidomide is a synthetic derivative of glutamic acid. It was marketed in Europe in 1957 as a sedative but withdrawn four years later after being associated with severe human teratogenicity: Thalidomide causes limb defects by suppression of blood vessels growth in the developing fetal limb bud. Thalidomide inhibits VEGF-induced corneal neovascularization in rodents. The Thalidomide trial has not proven that it is beneficial in slowing the rate of abnormal vessel growth in neovascular AMD (26, 34).

Integrins
Integrins are cell surface adhesion molecules that serve as receptors for extracellular matrix components or for other cells. Integrins help regulate processes such as cell proliferation, migration and differentiation.

It is known that integrins play a role in the unscheduled programmed cell death of newly sprouting blood vessels. Integrins are observed in CNV in AMD. In a murine model a systemically administered cyclic peptide antagonist of certain types of integrins specifically blocks new blood vessel formation with no effect on established blood vessels. The role of inhibitors of integrin in the treatment of neovascular AMD has yet to be tested (62).

Vascular Endothelial Growth Factor

The RPE produces vascular endothelial growth factor (VEGF), a glycoprotein that mediates retinal neovascularization in ischemic retinopathies. It is known that VEGF is associated with CNV due to AMD, however a causal relationship has yet not been identified. VEGF elicits its effects mainly via direct action on relevant endothelial cells (2, 11, 27).

III.6 SURGERY

III.6.a Submacular surgery for CNV

It is now possible to make an incision in the retina and remove subretinal new vessels and their accompanying fibrous tissue transvitreally. The objective is to do this without irreversible damage to the overlying retinal pigment epithelium, neurosensory retina or the underlying Bruch's membrane. Absence of RPE leads to atrophy of the underlying choriocapillaris and overlying neuroretina (24). The Submacular Surgery Trial Research Group was formed in America to conduct randomized clinical trials to evaluate whether submacular surgery stabilizes or improves visual acuity when compared with observation in patients with AMD.

Sofar major problems are: minimal improvement of visual acuity shortly after the surgery (the neovascular complex is intimately associated with the underlying retinal pigment epithelium resulting in its consistent removal of the epithelium at the time of surgery), potential risk of cataract, retinal detachment, recurrent membrane, endophthalmitis. The financial cost to the patient should also be considered.

Subretinal hemorrhage has been shown to cause retinal damage through three mechanisms: chemical toxicity (iron, vascular endothelial growth factor), mechanical traction on the photoreceptor outer segments, and establishment of a diffusion barrier. Surgery has been advocated if large subretinal hemorrhages associated with CNV occur, causing an obvious elevation of the retina. Surgical techniques for evacuation of subretinal hemorrhages are not limited to vitrectomy and internal drainage, with or without subretinal Tissue Plasminogen Activator injection and lavage (10, 20, 21, 39,44). One of several factors that limit visual recovery after submacular surgery is atrophy of the subfoveal choriocapillaris. It has been shown that the area of atrophy can continue to enlarge one year after submacular surgery. This progressive enlargement of the area of choriocapillaris atrophy is due to incomplete repopulation of the surgical bed by RPE at the perimeter of the dissected bed. The RPE is inevitably removed during submacular surgery because of its intimate association with the neovascular complex. The rationale for RPE transplantation is to replace RPE removed at the time of surgery with healthy retinal pigment epithelium and thus prevent choriocapillaris atrophy and atrophy of the overlying photoreceptors. A factor that limits transplantation of a patch of RPE is that the transplanted RPE does not survive in the subretinal space because of immunologic rejection by the host. Immunosuppression is not as well tolerated in older patients compared to younger ones and thus are difficult to use. There is a major difference between the viability and functional status of transplants introduced into the subretinal space after removal of neovascular membranes and those introduced into a vascular space where the blood retinal barrier is intact. The former transplants survive and function for only a limited period of time (2 months) due to retinal edema because of immunologic rejection by the host. The latter transplants develop edema rarely and local function including foveal fixation, remains unchanged for long periods of time. RPE transplantation deserves further research in order to evaluate its therapeutic potential (3).

III.6.b Translocation of the macula

Machemer and Steinhorst published a paper about retinal separation, retinotomy and macular translocation. It was the first attempt to restore vision by a surgical approach in AMD. The technique allows rotation of the retina and translocation of the fovea. The goal is to place the central part of the retina away from areas of severely diseased pigment epithelium, Bruch's membrane and choriocapillaris complex and to translocate the central part of the retina to an area where pigment epithelium is less diseased. This way the retina can preserve his function. Proliferative vitreoretinopathy is probably the most severe complication. The technique is extremely difficult and several retina surgeons are improving the technique that was suggested by Dr. Machemer. Examples are: foveal transplantation (limited retinal translocation), foveal translocation with scleral shortening, foveal translocation with 360° retinotomy and relocation of the fovea after scleral buckling (15, 16, 19, 29, 30, 38, 64).

CONCLUSION

Globally it is estimated that there are 38 million persons blind. A further 110 million people have low vision and are at great risk of becoming blind. Insufficient data on blindness from causes such as diabetic retinopathy and AMD preclude specific estimations of their global prevalence (58).

Hogan sounded a warning note 30 years ago that the increase in the prevalence of AMD due to aging of the population will become a major problem economically and socially (22). Studies in the United Kingdom and Japan have clearly shown that the increasing prevalence of AMD today cannot be explained by aging of the population alone (17, 69). There is not yet a preventive therapy that has a significant impact on blindness due to AMD. There is no therapy for geographic atrophy. There are limited forms of therapy with the objective of destroying new vessels arising in the choroid and of limiting the visual loss. Translocation of the macula is not yet a form of therapy that is widely accepted. That is why there is a need for more effort to find ways that influence the survival of the complex photoreceptor - RPE - Bruch's membrane in the aging population.

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