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Review

Macular Degeneration and Treatment

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ABSTRACT

Macular degeneration is an important cause of visual loss in the elderly. While it has been a problem that has not been completely cured until recently, it has been possible to prevent the progression of the disease with some applications in the last few years and to delay the resulting visual loss.

Keywords: Age related macular degeneration, experimental studies, treatment.

MACULA DEGENERATION

Age-related macular degeneration (AMD) is the most important cause of central vision loss in people over 50 years of age.[1]

Nowadays it is known that macular degeneration occurs due to damage of neurons.[2] This disease occurs as a complicated degeneration of the macula involving the photoreceptor, retinal pigment epithelium, Bruch's membrane and choriocapillaris.[3,4]

The incidence was found to be 10% between the ages of 65-75 and 25% above the age of 75, so it is an important public health problem.[3,4]

Macular degeneration is divided into two main groups: exudative AMD and atrophic AMD. The exudative type accounts for about 10% of cases and is characterized by the formation of new vessels from the choroid located at the lower part of the macula. The atrophic type accounts for about 90% of cases and is characterized by a slow decline in vision over many years, photoreceptor loss and geographical atrophy.[5]

ATROPHIC TYPE AMD

Atrophic (non-exudative) AMD has retinal pigment epithelium and photoreceptor loss. It is characterized by the accumulation of yellow crystals called drusen in the macula, and retinal atrophy areas form large patchy geographic atrophy areas in later periods (Figure 1). Generally, visual loss develops over the years in the atrophic AMD, while the exudative type manifests more rapidly.[6]

Although atrophic type constitutes approximately 90% of all AMD patients, 80-90% exudative type is responsible for visual loss.[6]

Approximately 10-20% of atrophic AMD patients progress to exudative AMD.[6]

EXUDATIVE TYPE AMD

The exudative (neovascular) type is characterized by the formation of new vessels developing from the

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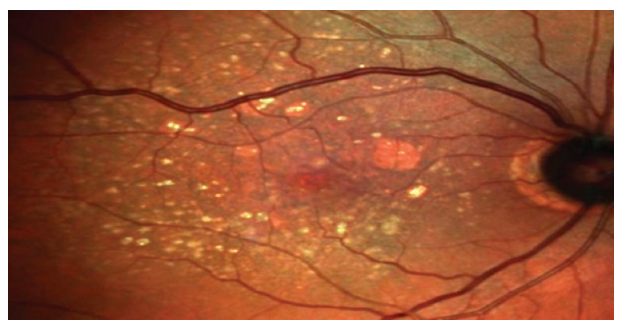

Figure 1. Yellow crystals called drusen appearing in the macula.[6]

pathological choroid under the retina in addition to retinal pigment epithelium and photoreceptor loss.[7]

Subretinal fluid, subretinal hemorrhage, retinal pigment epithelium (RPE) detachment causes symptoms such as central scotoma, metamorphopsy and reading difficulties (Figure 2).[7]

A typical symptom of exudative AMD patients is sudden onset and insidious, painless central visual loss. When subretinal hemorrhage develops due to the formation of a new choroidal vessel, the cases show sudden symptoms. However, when shallow subretinal fluid accumulation or retinal pigment epithelium detachment develops, the disease has an insidious course.[7]

EXPERIMENTAL AND CLINICAL TREATMENT STUDIES

Antioxidants and Vitamins

In the Age Related Eye Disease Study 1-2 (AREDS1-2) studies, a combination of 500 mg of vitamin C, 400 IU of vitamin E, 80 mg of zinc, 2 mg of copper, lutein and zeaxanthin has been shown to reduce dry AMD progression.[8-11]

Ongoing studies have shown that Crocetin is a carotenoid dicarboxylic acid derivative, experimentally inhibiting caspase activity, reducing oxidative stress and protecting against retinal damage caused by light exposure.[12]

In addition, pyridoxine (B6), folic acid (B9), and cyanocobalamin (B12), which are sub-classes of vitamin B, are known to reduce the risk of vascular disease by decreasing serum homocystine levels as well as antioxidant effects. A randomized clinical trial reported a reduced risk of AMD in individuals receiving B6, B9 and B12 daily.[13]

Visual Cycle Inhibitors

Agents of this class are used to reduce the accumulation of toxic products such as lipofuscin and N-retinylidene-N-retinylethanolamine (A2E) released by visual cycle and prevent the death of retinal pigment epithelium and photoreceptor cells.[14]

Fenretinide inhibits the formation of transthyretin-RBP complex by inhibiting all-trans retinol binding of retinal binding protein (RBP). Dose dependent-reversible reduction of RBP and retinol circulation reduces indirectly lipofuscin and A2E formation.[14]

A placebo-controlled study with this Phase-2 molecule showed a decrease in lesion development in patients with geographic atrophy after oral administration of 100 and 300 mg/day. In addition, a 45% reduction in choroidal neovascularization was observed in the group receiving Fenretinide irrespective of its dose.[14]

Anti-Inflammatory Agents

Dry type AMD, inflammatory deposits such as retinal pigment epithelial cells, bruch membrane and choroid lipofuscin have been shown to be effective in the process of chronic inflammation.[15-17] Therefore, the effect of corticosteroids on the anti-inflammatory and anti-angiogenic effects of dry type AMD is under investigation.[18]

The Iluvien, which is a molecule producted for this purpose, is an injectable form of corticosteroid implant in Phase-2 study in AMD patients.[18]

One of these agents, POT-4, binds to complement factor-3 and thereby inhibits the proteolysis required for C3a-C3b formation. The Phase-1 study of this molecule, which was administered intravitreally and has slow release effect was terminated in six months.[19]

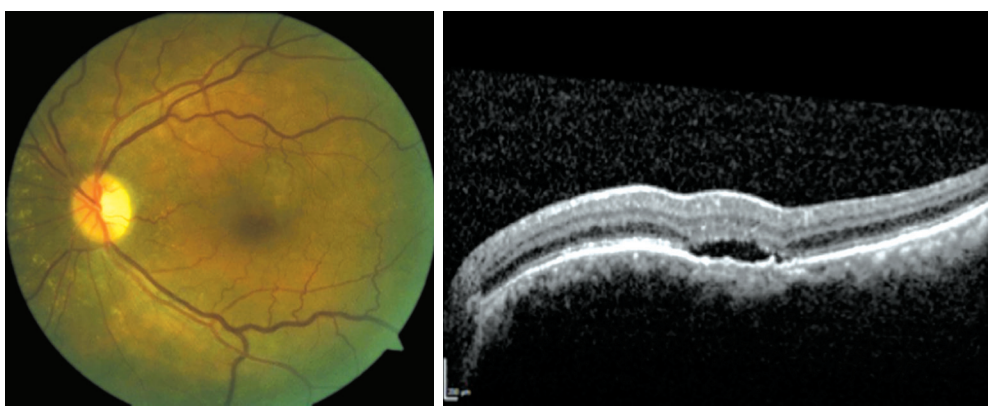

Figure 2. Retinal pigment epithelium detachment. Color fundus photograph and OCT image.[6]

Another agent, ARC-1905 is an anti-C5 aptamer which can be administered intravitreally and its Phase-1 studies are still in progress.[20]

Eculizumab is an approved molecule by FDA for its use in the treatment of paroxysmal nocturnal hemoglobinuria. This drug is a humanized monoclonal antibody that blocks complement factor-5 (C5) and is still in the Phase-2 study stage. However, when it's administered with an intravenous form in AMD patients, it did not show an effective change in the rate of geographic atrophy progression and drusen volume in a placebo-controlled Phase-2 study.[21,22]

The LGF-316 molecule is an another anti-C5 antibody which can be administered intravitreally. The results of Phase-2 study have not yet been published.[23]

The lampalizumab molecule is a monoclonal Fab fragment produced against factor-D in the alternative complement pathway. As a result of the Phase-2 study of this intravitreally administered molecule, 143 patients with bilateral geographic atrophy were followed up with 5mg, 10 mg and sham treatment monthly and in every two months. Although the effect started in the first six months, a 24% decrease in the progression of geographic atrophy was found at an average follow-up of 18 months.[24]

After monthly injection of lampalizumab, geographical atrophy patients with a complement factor inhibitor (CFI) mutation showed a 44% reduction in the progression of geographic atrophy over an 18-months period.[24,25]

One of these agents, GSK933776, is a monoclonal humanized antibody produced against intravenously administered β-amyloid. This antibody has been shown to reduce the accumulation of Beta-amyloid and C3a in the Bruch's membranes of mice. The Phase-2 study is still ongoing.[26]

Choroid Blood Flow Regulating Agents

It is thought that decreasing choroidal blood flow that provides oxygen and feeding environment to the outer retina layer with advancing age may play a role in the pathogenesis of AMD. Choroidal blood flow regulating agents have been developed for this purpose.[27]

MC-1101 molecule is produced in topical drop form and increases the choroidal blood flow by triggering the production of nitric oxide which causes the dilation of the vessels. As a result of the Phase-1 study, it has been pointed out to increase the choroidal blood flow velocity and volume in AMD and also have anti-inflammatory and anti-oxidant effects.[27]

Moxaverine molecule is a phosphodiesterase inhibitor that increases the choroidal mean flow rate in the ophthalmic artery and posterior ciliary artery.[28]

Stem Cell Transplantation

Another form of treatment is stem cell transplantation. Two different studies are carried out in this field. The first one is the Advanced Cell Technology (ACT) method, which uses human embryogenic stem cells.[29]

There are two separate Phase 1-2 studies evaluating retinal pigment epithelium-induced human embryogenic stem cell therapy in dry type AMD and Stargart macular dystrophy. The first study was a subretinal infusion of MA09-hRPE cells. The second study was a Phase 1-2 study evaluating the tolerability and safety of MA09-hRPE cell therapy in advanced dry AMD patients.[30]

CNTO 2476 is a method that uses umbilical-derived stem cells. Stem cells are injected subretinally by microcatheter and endoscope by external approach. The Phase 1-2 study is still ongoing in patients with geographic atrophy.[22]

In conclusion, anti-VEGF drugs are the most current treatment option that can be used safely in the treatment of AMD. Although the treatment modalities, which increase the injection intervals after loading treatment with three monthly injections other than monthly injection, are tried, however the best results are obtained with monthly injection treatments.[22,25-30]

However, monthly injection reduces patient compliance due to the risk of complications and the need to monitor patients frequently. When evaluated in terms of efficacy, the results obtained from the studies and clinical applications are still far from being satisfactory and it is possible to control serious visual loss with these treatments.[22,25-30]

Although there is a long way to go, many promising treatment options are being developed for both types of the disease. Among these studies, especially molecular studies on neuroprotection and stem cell studies are thought to be promising for the future.[22,25-30]

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