Is Dry AMD Treatable?

A new ophthalmic solution may halt disease progression.

BY GEORGE CHIOU, PHD

Several leading eye diseases such as glaucoma, diabetic retinopathy (DR), and age-related macular degeneration (AMD) cause visual disturbances within huge patient populations. Among them, dry AMD is the only one that does not have any approved treatment drugs worldwide. Numerous attempts have been made to treat dry AMD, either with physical or pharmacologic means, but all have failed.[1] Various attempts have been made to elucidate the etiology of dry AMD and to treat the disease by using agents that inhibit disease-causing factors. Unfortunately, there are too many factors involved in developing dry AMD. Eliminating only 1 or 2 factors does not produce significant suppression of disease development. Further, all disease-causing factors, such as drusen, lipofuscin, vascular endothelial growth factor, pigment epithelium derived factor, complements, leukotrienes, prostaglandins, and platelet activation factor, are waste products of normal physiologic processes. Complete suppression of these processes would result in serious side effects.[2]

NEW APPROACHES

Feces and urine are normal waste products of the body and are toxic unless they are excreted. When the excretion of feces and urine is blocked or reduced, serious diseases develop as a result. It has been found that dry AMD is caused by ischemia of choroidal blood flow. Consequently, various metabolic wastes are accumulated in photoreceptor cells, Bruch membrane, and retinal pigment epithelium (RPE) cells. In turn, these critical visual cells degenerate, dry AMD develops, and vision is reduced (Figures 1 and 2). If choroidal blood flow is resumed and metabolic wastes are excreted, the visual disturbances would be halted and/or reversed (Chiou Syndrome; Figure 3). This approach would more efficiently return the visual cells to normal function and would be more effective than using various agents to suppress the production of numerous metabolic wastes.

PRECLINICAL ANIMAL STUDIES

MC-1101 (hydralazine, MacuClear Inc.) is a clinically used, topically delivered treatment for stopping the

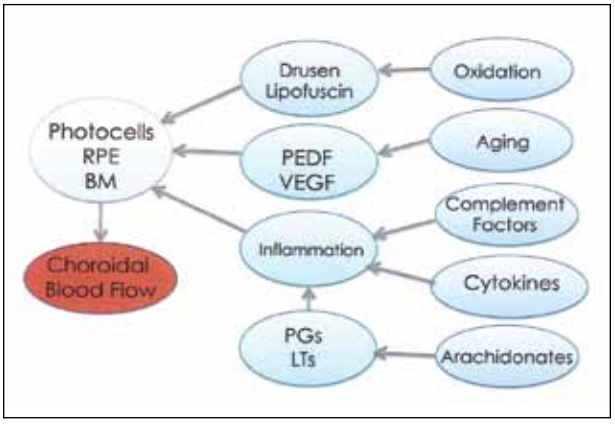

Figure 1. Natural effects on choroidal blood flow (CBF).

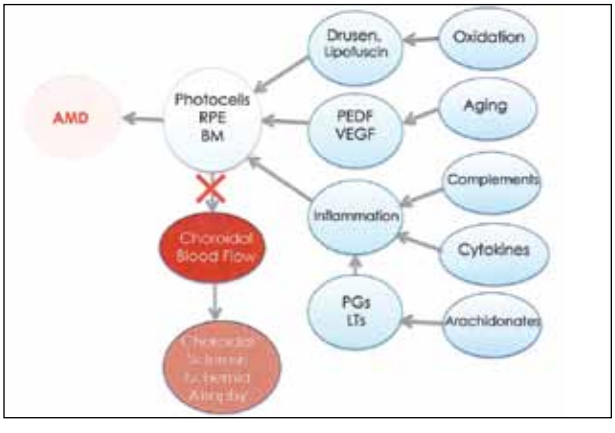

Figure 2. Metabolic pathways resulting in AMD.

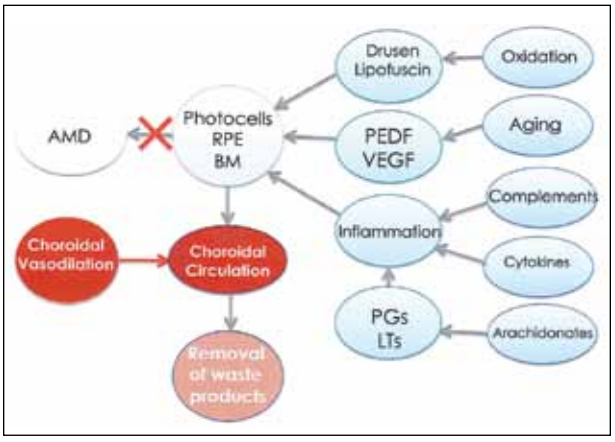

Figure 3. Summary of how restoration of CBF prevents progression of AMD.

progression of dry AMD. Because its active pharmaceutical ingredient has been used for decades as a systemic antihypertensive agent in the clinic, it is qualified for 505 (b)(2) status and fast track eligibility. MC-1101 has been shown to increase choroidal blood flow in ocular hypertensive rabbit models measured with colored microsphere technique[3] and to facilitate retinal function recovery following ischemic insult in rat eyes, as measured with electroretinography (ERG) b-waves.[3] Also in rat models, MC-1101 has been found to antagonize ERG c-wave reduction induced by RPE degeneration caused by $NaIO_3$[4] and to minimize laser-induced choroidal neovascularization (CNV).[3] No significant ocular toxicity was observed in 28 days of daily administration of topical ophthalmic solutions with Draize test in rabbit eyes.

PHASE 1B STUDY

The development of MC-1101 began in an effort to find a topical treatment for glaucoma.[5] To this end, 0.03% and 0.1% solutions were instilled into the eyes of 20 healthy human individuals to study their toxicity.[6] It was found that with either dose, there was no significant change in systemic blood pressure or pulse. Further, no significant breakdown of blood-aqueous barrier was noted. In most individuals, however, it caused a brief, mild to moderate conjunctival hyperemic response. Unlike in animal experiments, these concentrations caused slight increase of IOP rather than reducing it. As a result, the attempt to use this drug for glaucoma treatment was abandoned. Additionally, results indicate that acute topical instillation of 0.1% to normal human eyes does not cause clinically significant cardiovascular effects or significant ocular toxicity.

Further development continued, and similar clinical trials were carried out using MacuClear[7] with tenfold higher concentrations (1% ophthalmic solution) than before and aimed for the treatment of dry AMD rather than glaucoma.

In a phase 1b clinical trial, topical instillation of 1% MC-1101 produced no significant cardiovascular effects or ocular toxicity; no effect on the blood-eye barrier was noted; and no ocular effect on the contralateral eye was observed. It was concluded that topical instillation of MC-1101 acts locally on the treated eye, with no systemic action of the drug absorbed following ocular instillation.

The 1% concentration used was safe in this study. Ocular administration of 50 µL of 1% solution is equivalent to 0.5 mg in the eye or 0.007 mg/kg in a 70-kg patient. The usual systemic dose of the active pharmaceutical ingredient is 200 mg per day for a 70-kg patient or 1.4 mg/kg. In other words, topical administration of MC-1101 is equivalent to 1/200 of the systemic dose. Thus, no noticeable systemic side effects can be expected.

The results indicated that MC-1101 ophthalmic solution is safe and well tolerated with a low incidence of adverse effects that were generally mild in nature. There were no deaths and no other clinically significant safety findings during the course of the study. Ocular hyperemia was the most commonly reported ocular adverse effect noted. However, the ocular hyperemia is consistent with the peripheral vasodilatory effect of MC-1101 and was temporary in nature.

In order to verify MC-1101's mechanism of action, 1% MC-1101 was administered to the eyes of healthy individuals and patients with dry AMD. Choroidal blood flow was measured with laser Doppler flowmetry. It was found that MC-1101 reached the back of the eye at the macular area to improve the choroidal blood circulation following topical instillation. Because impaired blood flow may be a contributing factor in the progression of dry AMD, improvement of choroidal blood flow could result in removal of metabolic wastes from RPE, Bruch membrane, and photoreceptor cells to halt disease progression. Thus, MC-1101 may become a useful therapeutic drug for the treatment of dry AMD.[7]

CLINICAL ENDPOINTS

AMD is a chronic disease, and patients' visual acuities do not change dramatically during progression from the early stage (dry AMD) to the late stage (wet AMD). Consequently, the efficacy of a drug action cannot be assessed based on changes in visual acuity. There are a several parameters that may be used to objectively assess the progression of dry AMD, although they

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have not yet been approved by the US Food and Drug Administration.

Prolongation of dark adaptation is closely related to the severity of AMD[8-10] and is strongly affected in patients long before any significant loss of visual acuity occurs.[8] Thus, measurement of dark adaptation is an effective method for objectively assessing a drug's efficacy for the treatment of dry AMD.

It has been reported that rod photoreceptor degeneration precedes cone degradation in the early stages of AMD (dry AMD),[9,11-13] and rod dysfunction may contribute to the later degeneration of cones because of their interdependence.

RPE are critical cells to maintain normal function of Bruch membrane and photoreceptor cells. The degeneration of RPE cells can be detected by the measurement of c-wave of ERG, and the suppression of ERG c-wave can be used to noninvasively assess drug efficacy.[4,14]

Recently, it has been discovered that there is a close relationship between IP-10 (interferon-alpha inducible protein-10; also known as C7) and the progression of AMD.[15] Measuring the serum level of IP-10 in the test sample and comparing it with the reference level of IP-10 can determine the risk level of AMD development. Suppression of IP-10 with drug can be used to determine the drug's efficacy for the treatment of dry AMD. The reliability of this method is still under investigation.

Other testing methods are available, including the Ten-item Night Vision Questionnaire, the National Eye Institute Visual Function Questionnaire-25, number and size of drusen formation measured with Matched Flicker (EyeIC.com), and optical coherence tomography. The precise relationships between these methods and the progression of dry AMD still remain to be determined.

PHASE 2/3 STUDIES

MC-1101 is now in the stage of phase 2/3 clinical trials. A total of 500 patients are required for New Drug Application submission. The current study, which includes 60 patients, is designed to establish the efficacy of the drug and selected endpoints. If the results obtained are consistent, reliable, and significant, the data will be presented to the US Food and Drug Administration. Then the balance of required patients will be studied to complete the registration process for the New Drug Application. The entire process could take approximately 3 years.

CONCLUSION

MC-1101 ophthalmic solution has been found to increase choroidal blood flow, suppress dry AMD in animal models, and produce antioxidative actions in preclinical studies. It has also been shown to be a safe agent for ocular uses, and, when instilled in human eyes, it reaches the back of the eye at the macular area to increase choroidal blood flow. It is expected that MC-1101 could facilitate the excretion of metabolic wastes from RPE, Bruch membrane, and photoreceptor cells to halt disease progression. Thus, MC-1101 may have the potential to become the first drug for the treatment of dry AMD. ■

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