

# Research into AMD pathogenesis suggests new treatment and prevention strategies

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in Miami

RECENT research on the pathogenesis of exudative age-related macular degeneration (AMD) is suggesting new targets for innovative approaches to both treatment and prevention, according to Scott W Cousins MD, Bascom Palmer Institute, University of Miami, Miami, Florida, US.

"Angiogenesis inhibition is at the foundation of most ongoing clinical trials of investigational agents for the treatment of AMD-related choroidal neovascularisation.

However, there are a number of other paradigms for conceptualising this disease. Over the next ten years, we can expect those new ideas will fuel a pipeline of alternative interventions that will propel us into an exciting new era in the management of this potentially blinding disease," said Dr Cousins.

In his own laboratory, Dr Cousins and his co-workers have been focusing on the role of inflammation in the development of AMD-related CNV with special attention to the involvement of macrophages. Other research in this field is concentrating on contributions of various environmental factors, such as exposure to cigarette smoke, and systemic health factors, including hormonal influences.

However, among the new pathogenesis paradigms that are under investigation, Dr Cousins characterises the role of inflammation as the one most likely to first result in new therapeutic approaches.

"There are already a few clinical

trials underway investigating the use of anti-inflammatory drugs plus anti-angiogenic agents or other modalities, and we can expect that in a few years our management will be based on dual therapy rather than treatment with a single drug," Dr Cousins said.

Realisation that AMD may be an inflammatory disease is an extension of the growing recognition in medicine that inflammation and infection play an important role in the development of a variety of degenerative diseases, including Alzheimer's disease and atherosclerosis. With respect to AMD, two areas of intense research are the roles of complement and macrophages.

Dr Cousins and colleagues have documented the presence of blood-derived, highly activated macrophages in the retina and neovascular membrane in eyes with exudative AMD. Their studies in animal models of laser-induced choroidal neovascularisation show that treatment to deplete blood monocytes and lymph node macrophages was effective in decreasing choroidal macrophage density and CNV severity.

Dr Cousins speculates that the "savage" white blood cells have been recruited into the choroids from the circulation where they are playing a detrimental role in promoting progressive retinal degeneration rather than being helpful scavengers. That hypothesis has led him to develop a test for categorising AMD patients into risk groups based on analysis of the macrophages in blood specimens.

"Currently, we are studying the potential value of that test for identifying patients who would be

the best candidates for risk modulation with anti-inflammatory treatment," Dr Cousins said.

Also in the area of anti-inflammatory treatment for AMD, knowledge that verteporfin (Visudyne) photodynamic therapy elicits a significant inflammatory response has provided a rationale for studies of combination treatment with anti-inflammatory drugs. Results will be available soon from a recently completed, National Eye Institute-sponsored study that randomised patients undergoing PDT to treatment with celecoxib (Celebrex, Pfizer) or placebo. Celecoxib offers anti-inflammatory activity via its inhibition of cyclo-oxygenase-2, but of added interest, it appears to have anti-angiogenic properties as well.

Preliminary reports of data from that trial are encouraging, and meanwhile, results from a number of case series suggest a benefit from using intravitreal triamcinolone acetonide as an adjunct to PDT, he noted.

"More extensive trials are being planned for both of those dual approaches with the idea that a variety of different anti-inflammatory agents can be combined with PDT to improve the functional and anatomic results of that intervention," Dr Cousins said.

Related to the role of inflammation, there is also interest in the contribution of infectious agents to the pathogenesis of AMD. Against the background that both bacterial and viral agents have been implicated as triggers in promoting increases atherosclerosis severity, Dr Cousins notes that his group and other researchers have found the same provocative connection between the presence of exudative AMD and high antibody

titres for cytomegalovirus and the bacteria Chlamydia pneumoniae.

"One theory about the mechanisms of immune system amplification in AMD and other neurodegenerative diseases cites an infectious trigger. Confirmation of that association would suggest a possible therapeutic role for anti-infective agents, particularly as prophylactic intervention to prevent neovascularisation in high-risk AMD patients," Dr Cousins said.

Interest in environmental risk factors is centring particularly on cigarette smoke as accumulating evidence points to cigarette smoking as the most potent lifestyle risk factor for the development of both dry and wet AMD.

"It has been well-known for four decades that direct and passive exposure to cigarette smoke contributes to increased severity of a number of vascular diseases. As AMD is an ocular vascular disease, it is not unexpected that cigarette smoke is toxic to the macula," Dr Cousins said.

Results from animal models point to nicotine as playing a particularly harmful role in promoting progression of CNV. That information suggests that advice to patients about smoking cessation should include a recommendation about avoiding nicotine-based cessation aids, such as patches or chewing gum.

However, Dr Cousins notes that the role of cigarette smoke in AMD pathogenesis may have implications relevant to non-smokers, not only because of the hazards of passive cigarette smoke exposure but considering that of the 4,000 toxic substances com-

prising cigarette smoke, many are found as pollutants in the air of developed countries.

"Elucidation of the potential implications of that information is the focus of a number of investigators around the world," Dr Cousins said.

Just as the roles of post-menopausal oestrogen loss and oestrogen replacement therapy in cardiovascular disease have been the focus of many studies, so too is attention being directed to the effect of that hormone on AMD development and progression. For example, the Women's Health Initiative-Sight Exam study that is currently underway is evaluating the effect of oestrogen replacement on the risk of developing AMD-related blindness.

While the results from that trial are still pending, relevant preclinical studies show that loss of oestrogen predisposes female animals to more severe manifestations of macular degeneration, while treatment with pharmacological doses of oestrogen further exacerbates the pathology.

"Currently, it remains unclear what to recommend to AMD patients about oestrogen therapy as well as about ingestion of soy and plant-derived phytoestrogen supplements that are being widely used as natural remedies for hot flashes. Hopefully, that information will be available soon so that we can better counsel our patients," Dr Cousins said.

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