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Editorial

Gene therapy in age-related macular degeneration

Rajendra Prakash Maurya[1,*], **Sneha Gupta**[1]

[1] *Regional Institute of Ophthalmology, IMS, Banaras Hindu University, Varanasi, Uttar Pradesh, India*

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Age-related macular degeneration (AMD) is a multifactorial progressive degeneration of macula and it is the major cause of irreversible blindness in senile population in developed world. According to World Health Organization (WHO), about 10% of blindness is due to AMD. About 196 million individuals are affected by AMD worldwide.[1]

Several genetic and environmental risk factors are associated with AMD. Aging is the strongest non-modifiable risk factor whereas smoking, obesity, atherosclerosis, hypertension, hyperlipidemia are moderate and modifiable risk factors. Oxidative stress, altered hemodynamics, immune inflammatory responses play important role in pathogenesis of AMD.[2] AMD is usually classified into dry (non-exudative) and wet (exudative) forms. The dry form is more common comprising around 80 -90% of cases.

A positive family history increases the risk of AMD.[3] Klaver CC et al. reported one in four cases of advanced AMD is genetically determined.[4] Important genes implicated in AMD are: CFH (Compliment factor H), HTRA-1 (Htra Serine Peptidase-1) and ApoE (apolipoprotein- E) etc.[2] CFH inhibits multiple steps of the alternate pathway of inflammation. It binds with C-reactive protein (CRP) and inhibits the CRP-mediated response to photoreceptor damage. The Y402h mutation in the CHF gene may lead to complement dysregulation in AMD.[5–7] Single-nucleotide polymorphisms (SNPs) in chromosome 10q26 are associated with high risk of wet AMD.[8]

Ischemia-induced neovascularization of photoreceptor involves release of HIF-1 (Hypoxia inducible factor-1) and vascular endothelial growth factor (VEGF) that can be modulated by gene therapy.

rAAV2-sFLT1 treatment is used for prolonged management of neovascular AMD. Adeno-associated virus type 2 (AAV2)-sFLT1 combines a viral factor with plasmid which transduce retinal cells to produce highly potent naturally occurring anti VEGF (sFLT1=fms-like tyrosine kinase). Phase I/ IIa trial established safety and efficacy of rAAVs FLT1.[9] It improves central macular thickness and regain vision.

ADVM-022 / ADVM-032 - utilize a modified AAV2 vector which is specified for intravitreal infections, ADVM-022 expressing an aflibercept-like protein while ADVM-032 producing a ranibizumab like protein.[2]

Retinostat utilizes a recombinant equine infectious anemia virus (EIAV) vector which encodes two protein - endostatin and angiostatin through a subretinal injection. The phase-1 trial has been done for neovascular AMD without any adverse effects.[10]

AKST4290- is an oral treatment that targets against CCR3 which is receptor for eotaxin. Eotaxin is associated with membrane permeability in pathogenesis of AMD. Phase II trial showed improvement in BCVA of 2-83Y of wet AMD.[11]

* *Corresponding author*.
E-mail address: mauryarp_bhu@yahoo.com (R. P. Maurya).

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Author biography

Rajendra Prakash Maurya, Editor in Chief IJCEO, Associate Professor & I/c Orbit, Ocular Oncology and Oculoplasty Unit Regional Institute of Ophthalmology,
Institute of Medical Sciences,
Banaras Hindu University, Varanasi,(UP), India
E-mail: editorijceo@gmail.com, mauryarp_bhu@yahoo.com
https://orcid.org/0000-0001-9343-6003

Sneha Gupta, Junior Resident

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