Author's reply

Dear Editor,

We thank Khalili *et al*. for their valuable comments[1] in response to our article, "A comparative debate on the various anti-vascular endothelial growth factor drugs: Pegaptanib sodium (Macugen), ranibizumab (Lucentis) and bevacizumab (Avastin)".[2]

The recent study by Nishijama *et al*.,[3] recognized vascular endothelial growth factor (VEGF)-A as an important neuroprotectant in neural cell survival, in a model of ischemia-reperfusion injury. Ischemic preconditioning 24 h before ischemia-reperfusion injury increased VEGF-A levels and substantially decreased the number of apoptotic retinal cells. The protective effect of ischemic preconditioning was reversed after VEGF-A inhibition. Chronic inhibition of VEGF-A in normal adult animals resulted in loss of retinal ganglia. Therefore, it appears to be critical for retinal neuron survival, especially in response to ischemia in animal models. The clinical interpretation of this information would definitely point toward the importance of selective anti-VEGF agents in the context of ischemic retinal diseases.

Vascular endothelial growth factor-A, produced by a single gene on chromosome 6p21.3, consists of eight exons and seven introns, which produce as many as six different isoforms through alternative splicing, 121, 145, 165, 183, 189 and 206 amino acids in length. These different isoforms vary in their affinity for heparin binding and therefore in their affinity for the extracellular matrix. The larger isoforms, such as VEGF-189 and VEGF-206, bind heparin with high affinity and are therefore, almost completely sequestered in the extracellular matrix. The smaller isoform, VEGF-121, does not bind heparin and is freely diffusible.[4]

Another study[5] characterized VEGF localization in diabetic retinopathy using staining pattern of VEGF at different stages of diabetic retinopathy. They found that staining with the $VEGF_{165}$ antibody was generally confined to endothelial cells and perivascular regions, while the $VEGF_{121,165,189}$ antibody was also associated with extravascular components of the inner retina.

It is likely that there is a spatial preference of different VEGF isoforms. It appears that ischemic retinopathies are likely to be more responsive to selective VEGF inhibition, while all isoforms of VEGF which may be responsible for proliferation can be localized to the subretinal space in exudative age-related macular degeneration (AMD). Even from a systemic safety perspective, selective inhibition is more important for ischemic retinopathies than it is in AMD. However, with the availability of selective as well as pan-VEGF blockade agents, the roles, indications and contraindications of each will require large, prospective, planned studies.

Manish Nagpal, *FRCS;* ***Kamal Nagpal,*** *MS;*
PN Nagpal, *MS, FACS*

Retina Foundation, Ahmedabad, Gujarat, India.

Correspondence to Dr. Manish Nagpal, Retina Foundation, Shahibag, Ahmedabad - 380 014, Gujarat, India.
E-mail: drmanishnagpal@yahoo.com

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