

Asia Pharma 2016 : Development of novel antiangiogenic agents for the treatment of retinal neovascularization - Young-Ger Suh - Seoul National University

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The development of neovascularization and vascular leakage is one of the key pathological processes that leads to sight threatening complications in nearly all retinal vascular diseases including diabetic retinopathy, age-related macular degeneration, and retinal vein occlusion (RVO). Neovascularization is characterized by the growth of blood vessels that are morphologically and functionally abnormal. Neovascular blood vessels can be highly proliferative but are often structurally deficient and poorly organized as compared with normal, mature vessels. This may result in fragile neovascular fronds that tend to grow on the surface of the retina without the branching pattern characteristic of normal retinal vessels. The use of antiangiogenic agents for the treatment of various retinal diseases has recently emerged as a potential adjunct to standard ophthalmic care for ocular neovascularization. The majority of antiangiogenic agents with evidence of clinical efficacy at this time generally act by inhibiting vascular endothelial growth factors (VEGF). Anti-VEGF therapies have been shown to be remarkably effective in preventing vision loss from the neovascular and exudative complications of retinal diseases particularly in AMD and DR. Angiogenic factors have been shown to be central in the pathogenesis of proliferative retinopathies. Of these factors, VEGF has received the most attention in recent years and appears to be responsible for the majority of intraocular angiogenesis of ischemic origin. This is especially evident in ischemic retinal diseases such as proliferative diabetic retinopathy, rubeosis iridis, and central retinal vein occlusion. Other factors such as angiopoietin, erythropoietin, basic fibroblast growth factor (bFGF), insulin like growth factor (IGF), protein kinase C (PKC) enzymes, TGF, PDGF, and others may have moderating roles. VEGF-A is a heparin-binding homodimeric glycoprotein of 45 kDa. The human VEGF-A gene is organized in eight exons, separated by seven introns. Alternative exon splicing results in the generation of four different isoforms: VEGF121, VEGF165, which is the most prevalent human form, VEGF189 and VEGF206. VEGF secretion is dramatically induced by hypoxia (Dor et al. 2001; Semenza 2003) as are other growth factors (epidermal growth factors, TGF, IGF, and PDGF) and some hormones (TSH, ACTH, hCG, and sex hormones). VEGF is associated with breakdown of blood-retina barrier and increased vascular permeability of the retinal blood vessels. There are three main mechanisms by which antiangiogenesis agents are used for the treatment of proliferative retinopathies. These mechanisms include: (1) Inhibition of VEGF through direct binding; (2) Inhibition of VEGF synthesis; and (3) Inhibition of VEGF signaling. Currently there are four agents that inhibit of VEGF through direct binding that are being evaluated or used for the treatment of proliferative retinal diseases: Pegaptanib, Bevacizumab, Ranibizumab, and VEGF Trap. Pegaptanib is a pegylated ribonucleic acid aptamer that specifically binds human VEGF165 with high affinity. Bevacizumab is a humanized form of the

murine anti-VEGF-A antibody. It can block all forms of VEGF-A. It was originally FDA approved for treatment of metastatic colon cancer, and has since been approved for chemotherapeutic use in multiple other cancers. It is not FDA approved for any ocular indication.

There are two main types of AMD: nonneovascular and neovascular. Nonneovascular AMD is characterized by the presence of hard or soft drusen and retinal pigment epithelial (RPE) changes. Geographic atrophy of the RPE is present in advanced nonneovascular AMD. The pathology in AMD is a result of a combination of multiple mechanisms, some of which are not as yet completely understood. Oxidative stress is believed to be an important contributing factor to the development of AMD. Age-related inflammatory processes have also been implicated. Genetic variations in the factor H gene are highly associated with an increased risk of AMD. Photodynamic therapy (PDT), which uses the combination of photosensitizing agents and low energy laser to achieve selective destruction of CNVM, is another treatment option. PDT was the first treatment approach found to be effective by large randomized clinical trials for subfoveal lesions. Two major clinical trials, Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) and Verteporfin In Photodynamic therapy (VIP), showed that fewer patients in the PDT group lost 15 letters of vision as compared with the placebo group. Diabetic retinopathy is the leading cause of visual loss in the working age group in the United States and other developed countries. Visual loss from diabetic retinopathy is primarily caused by complications arising from neovascularization in proliferative retinopathy (PDR) or exudation and retinal thickening associated with the development of diabetic macular edema (DME). The introduction of pharmacologic treatments targeting antiangiogenic factors has revolutionized the management of proliferative and exudative complications of the most common sight threatening retinopathies. Based on the results of large multicenter randomized controlled clinical trials, intravitreal injection of anti-VEGF agents are now emerging as part of first line treatment in AMD, RVO, and DME. In addition, they are already considered a valuable adjunct in other conditions such as PDR and NVG with ongoing studies that may further define their role and benefits. Antiangiogenic agents have been used successfully in the treatment of sickle cell retinopathy, radiation retinopathy and other similar proliferative retinal vascular diseases. However, the long-term safety and potential toxicity of chronic VEGF inhibition needs to be closely monitored. A large and rapidly expanding body of angiogenesis research is accumulating from the efforts of multiple investigators around the globe. This information is helping define specific roles for different angiogenic factors and improved treatment modalities and therapeutic regimens. The forthcoming availability of numerous

highly specific antiangiogenesis agents and robust clinical trial data demonstrating remarkable efficacy is rapidly revising our current concept of standard care and holds great promise for improved management of these conditions in the near future.

Biography :

Young-Ger Suh is a Professor of College of Pharmacy, Seoul National University, South Korea. He was graduated from Seoul National University with BS degree in Pharmacy in 1975 and received PhD degree from University of Pittsburgh in 1987. Currently, he is a

President of Korean Society of Organic Synthesis, a full Member of The Korean Academy of Science and Technology, a Fellow of Asian Federation for Medicinal Chemistry and Vice President of The Korean Federation of Science and Technology Societies. He has published more than 150 papers in reputed journals and presented more than 200 papers at scientific meetings.

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