Erythropoietin strongly linked with proliferative diabetic retinopathy

Devon Schuyler

THE discovery of elevated levels of intraocular erythropoietin in patients with proliferative diabetic retinopathy suggests a new target for treatment, say Japanese researchers.

"This is the first study to examine erythropoietin as an angiogenic factor in diabetic retinopathy," Hitoshi Takagi MD, of Hyogo Prefectural Amagasaki Hospital, Japan, told *Euro Times*.

The researchers approached all patients undergoing pars plana vitrectomy at two Japanese hospitals between June 1997 and September 2004. They recruited 73 patients with proliferative diabetic retinopathy and 71 patients with nondiabetic ocular diseases. All patients gave samples of vitreous fluid, and some patients gave blood samples. Levels of erythropoietin and VEGF in the vitreous fluid were measured using a radio-immunoassay and an enzyme-linked immunosorbent assay, respectively.

The median level of erythropoietin in the vitreous was significantly higher in people with proliferative diabetic retinopathy than in those without- 464.0 mIU per millilitre versus 36.5 mIU per millilitre. The median level of VEGF in the vitreous also was significantly higher in people with proliferative diabetic retinopathy than in those without- 345.0 pg per millilitre versus 363.9 pg per millilitre.

In addition, the levels of erythropoietin were significantly higher in people with active retinopathy than in those with quiescent disease. There was a weak correlation between levels of erythropoietin and VEGF in the vitreous. A multivariate analysis revealed that erythropoietin was more strongly associated with diabetic retinopathy than was VEGF.

Analysis of the blood samples from 36 people with diabetic retinopathy and 42 without revealed that the median plasma level of erythropoietin was slightly lower in the diabetic retinopathy group and no significant correlation was observed between the vitreous and plasma levels of erythropoietin. This finding suggests that increased erythropoietin levels in the vitreous fluid result from increased production of erythropoietin in the retina, according to the study authors.

May have larger role than VEGF

The most surprising finding of the study, according to Dr Takagi, was that erythropoietin was associated more strongly than vascular endothelial growth factor (VEGF) with proliferative diabetic retinopathy. Vascular endothelial growth factor has long been known to promote retinal angiogenesis, although inhibition of VEGF does not prevent retinal neovascularisation. This fact led Dr. Takagi and his colleagues to suspect that other angiogenic factors are at work in diabetic retinopathy.

The researchers also conducted animal studies that revealed useful information. They exposed litters of seven-day-old mice to oxygen for five days before returning them to room air, while a control group was kept in room air. On days 12 and 14, the researchers injected soluble erythropoietin receptor, soluble VEGF receptor (soluble Flt-1-Fc chimera), both proteins, or heat-denatured erythropoietin receptor into the vitreous of the mice. As a control, researchers injected human IgG into the contralateral eye on the same days. Measurements were taken on day 19.

The researchers found that blocking soluble erythropoietin receptor was effective in inhibiting retinal neovascularisation, and that higher doses of soluble erythropoietin receptor led to greater inhibition of retinal neovascularisation. For example, neovascularisation was reduced by 35% with 25.0 ng of soluble erythropoietin receptor, and by 45% with 250 ng of soluble erythropoietin receptor. Neovascularisation was reduced even further, by 70%, with a combination of soluble erythropoietin receptor and soluble VEGF receptor.

Potential drawbacks

Although it is possible that targeting both erythropoietin and VEGF could lead to improved treatments for diabetic retinopathy, this approach may also have drawbacks, according to an editorial by Lloyd Paul Aiello MD, head of Joslin Diabetes Center's Section on Eye Research and associate professor of ophthalmology at Harvard Medical School, Boston. First, inhibiting erythropoietin in people with retinopathy might have adverse effects because erythropoietin appears to play a role in protecting the retina. Second, even if erythropoietin and VEGF do have an effect, there are likely also additional factors at work in diabetic retinopathy.

James Handa MD, an associate professor of ophthalmology at Johns Hopkins Medicine in Baltimore, told *EuroTimes* that Dr Takagi's research raises some intriguing possibilities with regard to the future treatment of proliferative diabetic retinopathy. However, he agreed with Dr Aiello that blocking erythropoietin could have the unintended side effect of damaging the photoreceptors in the retina.

"If large amounts of erythropoietin blocker were to make their way into the circulatory system, it could have the potential to cause anaemia and even neurologic injury," he added.

One of the study's weaknesses was its relatively small size, said Dr Handa. In addition, the study did not determine whether elevated vitreous erythropoietin is a cause or an effect of proliferative diabetic retinopathy.

Dr Handa said that the next steps in research should be to determine whether erythropoietin in the vitreous is a contributing factor in proliferative diabetic retinopathy, and whether erythropoietin blockers are safe for use in the eye. He was hopeful that further research into the role of erythropoietin could lead to the development of new non-laser treatments for proliferative diabetic retinopathy, and called for more research into preventing diabetes-induced ischaemia.

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