Pharmacologic vitreolysis opens door to non-surgical treatment of vitreoretinal diseases

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in Sao Paulo

PHARMACOLOGIC vitreolysis is a new therapy that could greatly facilitate vitreoretinal surgery today, and offer the possibility of preventing serious vitreoretinal disorders in the future, according to Jerry Sebag, MD, FACS, FRCOphth.

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"Pharmacologic vitreolysis will help to facilitate surgery as it is currently performed in complex vitreoretinal interface pathologies, such as retinopathy of prematurity, PVR, macular holes and proliferative diabetic vitreo-retinopathy," Dr Sebag told a session of the World Congress of Ophthalmology.

These vitreolytic agents may ultimately eliminate the need for surgery altogether by inducing a prophylactic posterior vitreous detachment (PVD) so as to prevent anomalous PVD in diabetic patients and in the fellow eye of patients with retinal detachments and macular holes, noted Dr Sebag, of the VMR Institute in Huntington Beach, California and the University of Southern California.

Dr Sebag stressed the importance of preventing anomalous PVD, which occurs when the extent of vitreous liquefaction exceeds the degree of vitreoretinal interface weakening, resulting in traction exerted at the vitreoretinal interface. He noted that the untoward effects on the retina of anomalous PVD include haemorrhage, retinal tears and detachment, vitreomacular traction syndromes and some cases of diffuse diabetic macular oedema. Proliferative diabetic retinopathy can also be greatly aggravated by anomalous PVD.

Dr Sebag explained that the goal of pharmacologic vitreolysis is to treat and prevent anomalous PVD by inducing liquefaction and vitreoretinal dehiscence. The new generation of drugs seeks to induce innocuous PVD by two distinct mechanisms of action: by loosening the vitreoretinal adhesion and inducing vitreoretinal dehiscence or by breaking down the gel consistency of the vitreous and transforming it into liquid vitreous.

The role of vitreous in the pathogenesis of various retinopathies has been increasingly appreciated in recent years. Although vitreous is 98% water, it maintains a gel consistency owing to the presence of hyaluronan which renders viscoelasticity, and collagen which provides the structural framework, said Dr Sebag.

"During development, vitreous becomes a gel thanks to the action of intermediary macromolecules, particularly proteoglycans such as chondroitin sulphate and heparan sulphate, and a recently identified small leucine-rich repeat protein known as opticin," he said. Dr Sebag emphasised that both liquefaction and vitreoretinal dehiscence need to occur in tandem so that an innocuous PVD can result.

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In the periphery, for example, anomalous PVD results in retinal tears and detachments. At the optic disc and along the retinal vessels, anomalous PVD plays an important role in proliferative diabetic retinopathy and other cases of vitreous haemorrhage. In the macula, the splitting of the outer layer of the posterior vitreous cortex can result in vitreomacular traction and macular holes.

Of the vitreolytic drugs currently being developed, Dr Sebag said that dispase, a bacillus-derived neutral metalloprotease, has shown efficacy in separating vitreous from retina, but not liquefying the gel. He noted that a recent Brazilian study in rabbit and human eyes found that dispase caused retinal toxicity, perhaps due to the broad range of proteins subject to its enzyme action.

"Dispase seems to be effective because it digests fibronectin which is present in the extracellular matrix between the vitreous cortex and the internal limiting lamina of the retina, and it also digests type IV collagen, which is present within the internal limiting lamina itself," he said.

Another enzyme, chondroitinase that specifically cleaves chondroitin sulphate, has shown efficacy in achieving both of the desired effects of pharmacologic vitreolysis, i.e. liquefaction and vitreoretinal dehiscence, said Dr Sebag.

"This agent was studied through many animal models, through the primates. Ultimately human studies were performed in a phase I trial. We await the initiation of the phase II trial but I think there is a lot of excitement about this agent because it works at both the vitreoretinal interface as well as within the vitreous gel," he said.

Another drug, hyaluronidase, showed early promise as a vitreolytic agent but has not lived up to expectations in a clinical setting. The drug is effective at liquefying the vitreous but does not work at the vitreoretinal interface and does not induce PVD, said Dr Sebag. Although it recently failed a Phase III US Food and Drug Administration (FDA) trial to clear vitreous haemorrhage, a meta-analysis of pooled data from two different trials in the US and Europe claimed to demonstrate efficacy.

"Significantly the pooled data found that hyaluronidase cleared vitreous haemorrhage in one out of every three cases, while saline cleared it in one out of four cases. The pooled data in this meta-analysis was statistically significant, but not clinically significant, since a 33% effect is not very potent.

"In fact, one could postulate that what we should do is first inject saline and if that fails, then inject hyaluronidase," he said.

In a separate presentation, Anselm Kampik MD reported initial results from clinical trials currently under way in Europe indicate that microplasmin may well be the ideal enzyme to induce PVD in a dose-dependent fashion. Dr Kampik said recombinant microplasmin, a truncated form of the natural human protein plasmin, has shown effectiveness in inducing PVD without any damage to the retina.

"It is still early days but we are very confident at the moment that this substance might be very helpful in the future to treat diseases at the vitreoretinal interface and may to some degree in the future replace the need for surgery itself in diseases such as diabetic retinopathy," he said.

Looking at the overall trial data to date, Dr Sebag said it was becoming apparent that rather than employing a single broad-acting substance such as dispase or plasmin, a combination of highly specific agents, such as collagenase, hyaluronidase or chondroitinase may ultimately be safer and more effective.

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"It is likely that no single agent will meet all our needs and a combination of agents will be necessary – a sort of vitreolysis cocktail, where the relative concentration of the constituent components will vary depending upon the disease that is being treated, on the age of the individual and the severity of that disease. But I think it is very exciting that pharmacologic vitreolysis will begin by facilitating surgery as we perform it today and ultimately to eliminate the need for surgery by inducing a prophylactic PVD before the onset of advanced disease," he said.

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