

Eye drops for retinal disease – Future or fantasy?

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Nottingham uk I CHINA I MALAYSIA Neovascular retinal disease - leading cause of blindness

Same Scene Viewed By A Person With:



Normal vision

Diabetic retinopathy

Affects 25-50% of diabetic patients

The leading cause of blindness in working population

Wet Age related Macular Degeneration Leading cause of blindness in the UK





Normal retina by OCT



Human Retina













But.. DME is ~10% of diabetic retinopathy

Proliferative diabetic retinopathy

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More good news!



Eyes without baseline DME

Anti-VEGF works in proliferative diabetic retinopathy too for a bit



The bad news!





Why do we have to inject treatments







"Large" molecules can't penetrate through the cornea













Small molecules could theoretically penetrate

Small molecule VEGF inhibitors		
Sorafenib (Nexavar) Bayer/Onyx	Tyrosine kinase inhibitor	
Sunitinib (Sutent) Pfizer	Tyrosine kinase inhibitor	
Pazopanib (Votrient) GlaxoSmithKline	Tyrosine kinase inhibitor	
Axitinib (Inlyta) Pfizer	Tyrosine kinase inhibitor	
Vandetanib (Caprelsa) Astra Zeneca	Tyrosine kinase inhibitor	
Cabozantinib (Cometriq) Exelixis	Tyrosine kinase inhibitor	
Regorafenib (Stivarga) Bayer/Onyx	Tyrosine kinase inhibitor	

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Pazopanib eye drop

Yafai et al 2011

Czacky et al 2015

Group 1	Group 2	
Ranib :	Placebo	-4.0 -1.2 1.6
Ranib :	5mg/ml TID	-3.1 -0.3 2.5
Ranib :	5mg/ml QID	-2.4 0.4 3.2
Ranib :	10mg/ml BID	-3.5 -0.7 2.1
Ranib :	10mg/ml TID	-3.9 -1.1 1.6
Ranib :	10mg/ml QID	-3.6 -0.8 2.0
Placebo:	5mg/ml TID	-1.9 0.9 3.7
Placebo:	5mg/ml QID	-1.2 1.6 4.3
Placebo:	10mg/ml BID	-2.2 0.5 3.3
Placebo:	10mg/ml TID	-2.7 0.1 2.8
Placebo:	10mg/ml QID	-2.4 0.4 3.2
Placebo:	Ranib	-1.6 1.2 4.0
		-5 0 5
		Group 1 Better Group 2 Better

DREAM Drops Flop

MAY 04, 2016 Ellen Kurek

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Regorafenib (Stivarga, Bayer) is an oral anti-angiogenic agent approved by the FDA for the treatment of metastatic colorectal cancer. It is a multi-kinase inhibitor that targets vascular endothelial growth factor (VEGF2/3) receptors, which are known to play a primary role in the progression of wet AMD. It also targets platelet-derived growth factor · (PDGFR-·) receptors.

Because of these effects, a topical form of the drug was evaluated in 51 patients with neovascular (NV) or wet age-related macular degeneration in the DREAM trial, a combined phase 2a/b trial. However, the trial was terminated after phase 2a owing to a lack of

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Animal model of diabetic retinopathy Intravenous injection with blue dye

> VEGFb treatment

Normal Retina Diabetic Retina

VEGF a and b are from the same gene

RNA

All current VEGF injections are proteins (antibodies...) Cannot get into the eye without injection Sphinxes are small chemicals – drugs – that can cross into the eye

Blocking splicing can prevent leakage into the eye

As eye drops!!

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 Blocking splicing can prevent leakage into the DIABETIC eye – as eye drops! (in rats)

 (A) Day 0 - FFA
 (B) Day 1 - STZ dosing i.p. (C) Day 0 or 6 - SPHINX31 eye drops(1µM)
 (D) Day 7 - FFA

SRPK inhibitors penetrate in vivo - rabbit

So now:

1. Can we use eye drops to switch VEGF splicing in the human eye?

