Water-Drinking Test

Revival of an Abandoned Diagnostic Tool

SÃO PAULO – The water-drinking test is helpful to assess the IOP profile of glaucomatous patients.


Susanna

Remo Susanna Jr.

The water-drinking test was first described by Schmidt as a diagnostic tool for glaucoma[1]. However, it was later abandoned due to its poor diagnostic accuracy[2,3].

Growing Interest

Recently this test was revived with a new purpose. Studies have shown that the water-drinking test may be used as a surrogate for detecting patients who have IOP spikes not identified during office hours.[4,5] The water-drinking test has also been used to evaluate the effect of treatment on reducing IOP peak and fluctuation, both with ocular hypotensive medications and filtering surgery[6-13]. Also, the peak of the water-drinking test correlates with the severity of glaucoma[14] and a patients' response to the water-drinking test may be predictive of visual field progression[15-17].

There has been a growing interest in the water-drinking test among ophthalmologists. This test has been cited a mean of 10.26 times in the literature[18] and has been the title of three editorials in peer-review journals[18-20].

It has been used to assess the quality of treatment, and how a given eye is able to control its IOP. Also, the IOP peaks of the water drinking-test strongly correlate and are in agreement with IOP peaks that normally occur during the day.

This lecture will show the importance of this test to assess the IOP profile of glaucomatous patients and how it can be used to make therapeutic decisions. ■

Thu, 16 February 13.00 – 14.30 hrs
Hall 11
Session: GLA - Intermediate

Author: Remo Susanna Jr. MD
Professor and head
Department of Ophthalmology
University of São Paulo
Av. São Gualter, 99
05455-000 São Paulo SP - Brazil
Tel: +55(0)11-3022-2738
Fax: +55(0)11-3022-4300
E-Mail: rsusanna@terra.com.br

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Rapidly Evolving Field

New Therapies for Wet AMD

KARLSRUHE – The treatment of wet age-related macular degeneration (AMD) is the most rapidly evolving field in ophthalmology. Laser treatment was replaced by photodynamic therapy (PDT) which was able to reduce the vision loss significantly. Today we are already able to increase vision in wet AMD-patients either by using ranibizumab/bevacizumab or VEGF-Trap.

In addition, there are numerous treatments under investigation. Those approaches can be grouped according to the therapeutic target:

1. VEGF Cascade

Multiple molecular interactions finally result in the production of vascular endothelial growth factor (VEGF). A key step in the VEGF production involves a molecule known as mTOR (mammalian Target of Rapamycin), a protein kinase that regulates cell proliferation, motility, survival and protein synthesis. It leads to the activation of certain transcription factors, including hypoxia-inducible factor 1α (HIF1α), which activates several genes, including those that produce VEGF.

RTP801 (REDD1) is a gene that displays strong hypoxia-dependent upregulation in ischemic cells of neuronal origin. It promotes VEGF production through the mTOR/HIF1α pathway. RTP801i-14 (Quark/Pfizer), now known as PF-4523665, is a small interfering RNA (siRNA) that has been developed to inhibit REDD1 and suppress VEGF production as well as inhibit angiogenesis.

The signaling pathways are addressed by mTOR-inhibiton (Sirolimus (Rapamycin); Everolimus (RAD001); Palomid 529).

Sirolimus (Rapamycin) exhibits significant antitumor/antiangiogenic activity that is coupled with a decrease in vascular endothelial growth factor (VEGF) production and a reduction in the response of vascular endothelial cells to stimulation by VEGF.

Everolimus (RAD-001) is the 40-O-(2-hydroxyethyl) derivate of Sirolimus and works similarly to sirolimus as an mTOR (mammalian target of rapamycin) inhibitor. It is currently used as an immunosupressant to prevent rejection of organ transplants and treatment of renal cell cancer. Much research has also been conducted on Everolimus and other mTOR inhibitors for use in different cancers.

Palomid 529 (P529) is a novel potent antitumour PI3K/Akt/mTOR inhibitor. Palomid 529 (P529) inhibits the TORC1 and TORC2 complexes and shows both, inhibition of Akt signaling and mTOR signaling similarly in tumor and vasculature.

Palomid 529 (P529) inhibits tumor growth, angiogenesis, and vascular permeability. It has been shown that Palomid 529 (P529) inhibited both, VEGF-driven (IC50 = 20 nM) and bFGF-driven (IC50 = 30 nM) endothelial cell proliferation and retained the ability to induce endothelial cell apoptosis.

2. VEGF and VEGF-Receptor

Once VEGF is generated therapeutic agents which directly target the VEGF molecule (ranibizumab/bevacizumab or VEGF-Trap) are used. This is the most advanced approach.


Augustin

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More anti-VEGF molecules such as KH902 are currently under investigation. KH902 is a fully human fusion protein containing key domains from vascular endothelial growth factor receptors 1 and 2 with human immunoglobulin Fc.

Furthermore, there are several approaches under investigation to target the VEGF-receptor directly and/or integrins in general.

3. VEGF Effects

Following production VEGF binds to its receptors. By doing so the molecule initiates a series of events which are mediated by tyrosine kinase (tk). Thus, tk-inhibitors should be also efficient in counteraction VEGF-initiated effects in the tissue.

Currently the kinase inhibitors pazopanib and AL39324 are under investigation. So far the following clinical data is being generated for pazopanib in ophthalmology: A 28 day phase II study to evaluate the pharmacodynamic effect of pazopanib eye drops on the central retinal thickness of AMD patients has been performed. Currently, a phase IIb dose-ranging study is underway to investigate the efficacy of pazopanib eye drops in patients who are being treated with ranibizumab injections.

Additionally, a 12 week, open-label phase II study to investigate the safety and efficacy of a single dose regimen of pazopanib eye drops for neovascular age-related macular degeneration is being carried out.

4. Additional Pathways in the Angiogenic Cascade

Besides the VEGF-cascade tubulin-inhibition (Combretastatin, fosbretabulin, OX-10X), acting against sphingosine-1-phosphate (S1P) with potential antiangiogenic and antineoplastic activities (sonepcizumab), inhibition of pigment epithelium derived factor (Ad-PEDF) or Platelet-derived growth factor (PDGF; E1030) and complement inhibition (POT-4 (AL-78898A) are further promising therapeutic attempts.

Microtubules, a major type of cytoskeletal filament in cells, are formed from tubulin subunits, including α-tubulin and β-tubulin. They play an important role in cellular functions, such as replication, cell movement and organelle transport. Thus, antagonization of those molecules should exert an antiangiogenic effect.

Sphingosine-1-phosphate (S1P) is a bioactive lipid molecule that stimulates endothelial cell migration, proliferation, and survival in vitro, and tumor angiogenesis in vivo. Again, targeting this molecule should reduce proliferative activity.

POT-4 (Potentia Pharmaceuticals, Inc.), a small molecule derivative of Compstatin is directed against complement factor C3. POT-4 is a cyclic 13 amino acid peptide, which interferes with the cleavage of C3, the component all 3 pathways of complement activation converge on. It is the first complement inhibitor studied in patients with AMD. POT-4 has completed phase 1 testing in patients with wet AMD with an excellent safety profile. A unique feature of POT-4 is that it persists as a long-lasting gel deposit after intravitreal injection. The study demonstrated that significant levels of drug are maintained in the vitreous cavity for up to 6 months following a single injection. A phase 2 study is currently under way.

Genentech/Roche is working on anti-factor D (FCFD4514S) that inhibits the C3 and C5 alternative pathway convertases. Phase 1 studies have been successfully completed.

Furthermore, two C5 inhibitors are being studied: Eculizumab/Sollris (Alexion) and ARC1905, an anti-C5 aptamer (Ophthotech).

In summary, the inflammatory cascade plays a significant role in this disease entity. Therefore, targeting this part of the pathway could be a very effective approach in the future of wet AMD treatments.

5. Vitreoretinal Traction

This part of the disease entity has been underestimated so far. The elimination of vitreoretinal traction by means of surgery or with a vitreolytic agent therefore can be reasonable when traction contributes significantly to the disease process. In those subjects who are not responding adequately to anti-VEGF the vitreous body should be investigated in detail. A prospective trial to investigate this approach is pending. ■

Fr 17 February 13.30 – 15.00 hrs
Capital Suite 13
Session: PHA - Drugs for posterior segment disease

Author: Prof. Dr. Albert J. Augustin
Städtische Klinikum Karlsruhe
Moltkestr. 90
76133 Karlsruhe
Germany
Tel: +49(0)721-974-2010
Fax: +49(0)721-974-2009
E-Mail: albertjaugustin@googlemail.com