Shifting Focus in Ophthalmic Clinical Research

PEER REVIEWED

The ophthalmic research generating the most "buzz" over the past two decades has been for neovascular retinal disorders with consecutive approvals of incrementally improving therapies. In the year 2000, photodynamic therapy (PDT) with verteporfin replaced laser photocoagulation for treatment of wet age-related macular degeneration (AMD), and this quickly became the standard of care, while still leaving huge opportunity for better treatment options. PDT did nothing to improve vision and showed only limited success for select patients in maintaining the vision loss that had already occurred at the time of therapy[6,30].

So on came the vascular endothelial growth factor (VEGF) inhibitors[33], led by the approval in 2004 of pegatanib sodium injection for wet AMD which briefly replaced PDT as the standard of care. This was subsequently unseated by ranibizumab in 2006, the anti-VEGF antibody fragment derived from the full molecule bevacizumab which had been studied (and is approved) for various oncology indications. Thus was launched the "great debate" over the past five years between the two monoclonal antibodies: although bevacizumab is not approved in any ophthalmic indication, its off-label use has shown similar efficacy and safety at a substantially lower cost[8,37]. In early 2011, ranibizumab received EU approval for a label extension to include treatment of diabetic macular edema (DME) and regulatory submissions for the same are underway with the FDA. Lastly, the newest VEGF-inhibitor, aflibercept, which has shown similar efficacy to ranibizumab and bevacizumab in clinical trials[37], was approved by the FDA in November 2011 for wet AMD; it is currently under review in the EU for AMD, and under investigation globally for DME. Regardless of their formal approvals, it should be noted that physician-prescribed use of all the VEGF inhibitors has become the standard of care for DME, retinal vein occlusion, diabetic retinopathy and other retinal disorders as well[27].

Though there is room for improvement with regard to reducing the frequency, decreasing the cost[12] and developing a less invasive delivery method for treating neovascular eye disease, the reality is that there are multiple viable options available for physicians and their patients. The "war" to treat these diseases is all but over, with less reason to pursue new monotherapies[36].

Flying below the radar during this same period, there continues to be research for new therapies in other eye diseases. We are experiencing a resurgence in clinical stage investigation for eye diseases that currently have suboptimal standard of care. This includes, in particular, glaucoma, for which new neuroprotective agents are under investigation to complement or even replace traditional intraocular pressure (IOP) lowering therapies, and dry eye disease (DED), for which there is an improved understanding of the inflammatory nature of the syndrome. Both disorders have long had methods for treating the symptoms, but there is growing research to find therapies to resolve their underlying causes.

Neuroprotection in Glaucoma

Glaucoma is a group of diseases resulting in damage to the optic nerve and ganglion apoptosis, which is initially manifested as visual field loss and, ultimately, irreversible blindness if left untreated[1]. A visual simulation of its effects is represented in Figure 1. Though typically accompanied by elevated intraocular pressure (IOP), this is merely part of the syndrome; glaucoma is more accurately described as an optic neuropathy resulting from death of retinal ganglion cells. Damage at the optic disc may result from a buildup of fluid in the anterior chamber and/or from systemic or localized hypertension. As such medicinal, laser, and surgical options (see Figure 2) typically intend to reduce IOP and thus relieve tension within the eye[21].

Figure 1 – A scene as viewed by someone with normal vision compared to the lost visual field effects of a person suffering from optic neuropathy related to glaucoma (courtesy National Eye Institute, National Institutes of Health).

Standard of care pharmaceutical therapies include topical eye drops which aim to increase the outflow of aqueous fluid (prostaglandins or parasympathomimetics); hyperosmotics to decrease aqueous fluid production (beta-blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors); and epinephrine which does both. Current treatments are generally insufficient in resolving the visual consequences of the actual disease[2,21].

The latest introduced therapies have targeted the reduction of dosing frequency to once or twice daily and to provide a broad array of treatment options to physicians and their patients. Laser trabeculoplasty may also be used to improve the fluid outflow through the trabeculary meshwork, but multiple sessions are often required and the effect is generally limited to just a few years before retreatment or alternative therapy is sought. Conventional surgery may also be considered to physically create a new opening through which fluid may flow (see Figure 2)[20]. Alternatively, anti-hypertensives may be utilised to control blood pressure which may also have effects at the optic disc.

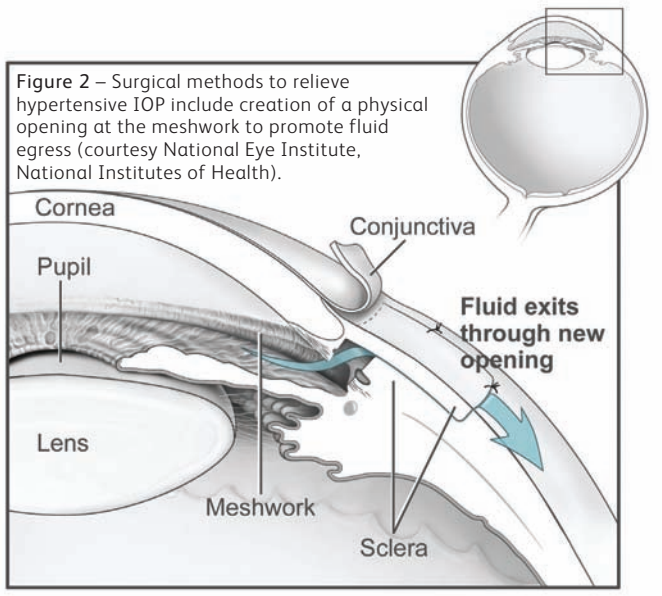

Figure 2 – Surgical methods to relieve hypertensive IOP include creation of a physical opening at the meshwork to promote fluid egress (courtesy National Eye Institute, National Institutes of Health).

More recently there has been increasing evidence of the ability to treat the actual optic nerve that is damaged as a result of glaucoma with various neuroprotective agents including phenytoin, brimonidine, epigallocatechingallate, ciliary neurotrophic factor and other proprietary formulations. This is of keen interest because there currently is no way to improve vision for those patients who have irreversible impairment as a result of long-term and/or significant ocular hypertension.

Neuroprotection – the term for nervous system mechanisms protecting neurons from apoptosis[34] – for glaucoma patients is not a new concept; published articles dating to the 1990s first introduced its viability[31,35]. However, the concept that has continued as a controversial pipedream for the past ten years is now gaining momentum[1] and advancing to the clinic. With current understanding that IOP-lowering by itself may not retard disease progression, there is significant interest in new modalities for treating glaucoma[34]. In fact, VEGF agents like those developed previously for retinal disorders are now being increasingly evaluated for certain types of neovascular glaucoma and other diseases[2,27].

As glaucoma is broadly of varied etiology, neuroprotective management would offer the additional benefit that the underlying cause and symptoms would become inconsequential to the treatment of the disease. That is, a universal neuroprotective treatment would, in theory, work on any glaucoma patient[35]. There is evidence that neuroprotection may be achieved pharmacologically by preventing stress on nerve cells resulting from their own toxic feedback mechanisms, or more directly by boosting the body's own immunologic abilities. Neuroprotective agents have long been under investigation for other central nervous system disorders including stroke, spinal cord injuries, Parkinson's disease and Alzheimer's disease, and these concepts are now trickling down into eye disease research[26]. With advancements in representative animal models to improve our understanding of the biochemical pathways affiliated with glaucoma, there is a growing body of laboratory and preclinical evidence for neurological targets to include glutamate receptors, autoimmune elements, neurotrophin deprivation, nitric oxide synthesis, oxidative stress products, sodium and calcium channels, heat shock proteins and apoptotic pathways[7,29]. Most human research, including the use of ciliary neurotrophic factor, brimonidine and siRNA technologies, is at the early stage in the clinic, often via investigator-led research, yet this has the potential to be an expanding field in the coming decade[16].

Dry Eye Disease Developments

Keratoconjunctivitis sicca (KCS) or dry eye disease (DED) is a multifactorial disorder of the tears and the ocular surface that results in symptoms including discomfort (burning, itching, pain), visual disturbance, foreign body sensation, light sensitivity (photophobia), and tear film instability with potential damage to the ocular surface[10]. Aqueous tear deficiency (ATD) is the most common cause of DED impacting the tear layer which covers the normal ocular surface and serves as a surfactant, as an aqueous barrier to retard evaporation, and provides a smooth optical surface.

DED is a common disorder whose prevalence increases with age and has been estimated to affect up to 10% of non-contact wearers and up to 50% of those who wear contact lenses[4]. DED can be classified as Sjogren's syndrome-related versus other causes. DED also particularly affects postmenopausal[11] or pregnant women and females taking oral contraceptives or hormone replacement therapy (especially estrogen-only pills). Also, certain systemic medications, such as antihistamines or beta-blockers, tend to decrease tear production leading to dry eye syndromes. Incidence among industrialised countries is comparable.

Dry eye is diagnosed via a combination of patient history and various tests, but no single assessment permits absolute diagnosis. Since DED is recently associated with structural or functional changes resulting from inflammation[10,32], the use of topical steroids or non-steroidal anti-inflammatory medications may be prescribed, and topical antibiotics may be necessary if the dry eye syndrome is associated with corneal complications; however, to date, approved therapies have been primarily limited to artificial lubricants with no impact on the underlying causes of DED, and, in more severe cases, topical immodulating therapy (cyclsporine). Restasis cyclosporine ophthalmic emulsion remains the only approved prescription pharmaceutical specifically labelled for DED, and it is only approved in the US with moderate improvement for tested research subjects. Not surprisingly, greater than 90 per cent of ophthalmologists indicate more and better treatment options are needed for DED[3].

With limitations in the efficacy and availability of DED therapies, there is great opportunity for improvement. Further, there is a wealth of recently developed knowledge about the underlying etiology of DED, including aspects of tear evaporation, insufficient tear production, tear film instability and the inflammatory basis for the disease allowing development of new pharmaceutical targets[5,11]. In addition, we are witnessing a growing wave of clinical investigational programmes targeting new methodologies of treating DED, including topical and oral anti-inflammatories, drug/device combinations, adjuvant therapies to and/or improved formulations of cyclosporine, and other novel approaches. A selection of leading clinical candidates summarised in Table 1 demonstrates over a dozen programmes that are in or approaching late-stage research[13-19,22-25].

Table 1 – Select clinic-stage investigational products for dry eye disease.

Sponsor Company	Investigational Product	Development Status	Mechanism
Alcon Research	Durezol (difluprednate ophthalmic emulsion)	Currently in Phase II	Topical anti-inflammatories for ocular use
	ESBA105	Currently in Phase II	
Altos Vision	AV 1 (17-β-estradiol)	Status unknown	Specifically targeted for postmenopausal women who make up 60% of dry eye population with data suggestive of tear osmolarity improvements
Eyegate Pharmaceuticals, Inc.	EGP-437 with EyeGate® II System	Completed Phase III	A drug / device combination using low voltage electrical current for iontophoretic delivery of dexamethasone phosphate
LuxBio Sciences (licensed for ophthalmic indications from Isotechnika Inc.)	LX214 (voclosporin)	Completed Phase I	Nanomicelle encapsulated delivery of ocular inflammatory therapy
Mimetogen Pharmaceuticals	MIM-D3	Completed Phase II	A small molecule tyrosine kinase receptor agonist acts to stimulate mucin secretion from conjunctival goblet cells
Novagali	Cyclokat (Ciclsporin A)	Completed Phase III	A cationic emulsion improves the absorption of Cyclosporine A in the cornea and conjunctiva
Novartis Pharmaceuticals	AIN457	Enrolling Phase II	Humanized monoclonal antibodies with anti-inflammatory properties delivered via IV infusion
	ACZ885	Enrolling Phase II	
OphthaliX Inc. (previously Denali Concrete Management, Inc., spun off from Can-Fite BioPharma Ltd.)	CF101	Enrolling Phase III	Orally-administered anti-inflammatory small molecule
Otsuka Pharmaceutical Co. Ltd. and Acucela Inc.	Rebamipide ophthalmic suspension	Completed Phase II	Stabilizes the tear film throuch increased mucin in the conjunctiva and cornea leading to the improvement of localized dry eye disease damage
RegeneRx Biopharmaceuticals, Inc.	RGN-259 (thymosin beta 4)	Completed Phase II	A Tβ4 eye drop promoting corneal epithelial cell migration and decreased ocular inflammatory properties
Resolvyx Pharmaceuticals	RX-10045	Completed Phase II	A synthetic resolving analog acting as a lipid mediator to reduce both acute and chronic inflammation
Santen Pharmaceutical Co., Inc.	DE-110	Completed Phase II	A selective glucocorticoid receptor agonist (SEGRA)
SARcode Bioscience, Inc.	SAR-1118	Enrolling Phase III	Inhibits T-cell response thus blocking the inflammatory cascade

Glaucoma and DED Clinical Research in Emerging Markets

Like many therapeutic areas, clinical research in eye diseases has frequently been limited primarily to North America and Western Europe. Historically, countries in these regions have trained physicians, educated and motivated patient populations and a clinical research support network to conduct eye disease trials. These countries are also utilised with consideration for the clear regulatory paths to marketing approvals with infrastructure readily in place for future sales distribution. Even today there remains an imbalance; a review of all active studies in glaucoma and DED reveals there are more ongoing trials in the US and Canada than all other countries combined, as demonstrated in Table 2.

Table 2 – Number of recruiting trials (courtesy ClinicalTrials.gov on 24 January 2012).

	Glaucoma	Keratoconjuctivitis Sicca (Dry Eye)
North America	91	31
Europe	34	9
Asia-Pacific	27	7
Middle East	14	1
South America	5	2

Though there is no shortage of interested ophthalmologists or patients in the US, Canada and Western Europe, clearly the clinical research space is far more saturated in these locations. Ophthalmic investigative sites in these regions are frequently saddled with multiple ongoing studies across all indications, even concurrently running studies that may compete for the same patient enrolment, with study coordinators dividing their attentions across many protocols. Thus, there is growing commercial interest in conducting eye disease research in emerging territories[28]. Considering the current challenges of the global economic downturn, there are great financial incentives to conduct a higher proportion of research in markets where financial hurdles may be lower.

For glaucoma, much of the neuroprotective research is still in preclinical stages. Thus, there are significant opportunities for investigator-led research which may be initiated from any location in order to discover or advance early therapeutic candidates. As expansion to human trials continues, there is need for more comprehensive multidisciplinary sites than what has been required for glaucoma studies historically. This is because new investigational therapies may require intravitreal injections typically performed by retinal specialists, or intravenous delivery, collaboration with other sub-specialists such as ocular immunologists and advanced diagnostics such as optical coherence tomography (OCT), confocal scanning laser tomography (CSLT), scanning laser polarimetry (SLP) and photographic imaging of the optic nerve head (ONH) for visualisation of damage and treatment effects at the back of the eye (9). Clinical sites who have been certified in protocol-conduct of diagnostic imaging and ETDRS best-corrected visual acuity assessments will have a "leg-up" at the feasibility assessment stage for new trials. As these technologies, training and expertise continue to expand to emerging markets, there will be greater interest to place industry-sponsored studies in locations that are less commonly used today.

For dry eye studies, the "barriers" to participation are typically low. Patients are frequently diagnosed and treated by general ophthalmologists, low-tech diagnostics are commonly employed, and procedures are generally non-invasive. And, with an aging global population over the next two decades, there will be a ready and growing patient pool for participation in DED clinical research; this is well-timed with the advancement in therapies as discussed previously. One technique that potential sites may consider performing regularly is measurement of tear osmolarity, as this has not been standard practice for DED in the past, but is expected to be a more frequently used assessment in future research.

With the frequency and clinical diagnosis of DED higher in the Hispanic and Asian populations than in the Caucasian population, emerging markets are ideally suited for conduct of research studies for new DED therapies.

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Nicholas Spittal, MBA, PMP, Associate Director, Global Clinical Development at Chiltern International, has been leading industry studies in ophthalmology for ten years, including directing the then-largest global programmes in three different retinal indications. Chiltern International is a global full service contract clinical research organization offering consultation and operational services to the biopharmaceutical industry, with particular expertise in eye disease research. Mr Spittal may be reached at
Email: nicholas.spittal@chiltern.com

David Hoelscher, MD, Clinical Research Physician at Chiltern International, has worked for over 19 years as a physician, principal investigator, and clinical researcher across a broad range of therapeutic indications. He is the Global Head of Chiltern's Therapeutic Area Team in Ophthalmology responsible for providing internal and sponsor-directed strategic guidance in the design and execution of Phase I-IV eye disease trials. Dr Hoelscher may be reached at Email: david.hoelscher@chiltern.com