New Pharmacological Treatments for Dry Eye Disease

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Abstract The impact of dry eye disease on patient's health, visual function and quality of life may be substantial. At present, the only approved pharmacological treatment in the U.S. or Canada is Restasis® (cyclosporine ophthalmic emulsion). In Japan, three products are approved: Hyalein® (hyaluronic acid), Diquas® (diquafasol), and Mucosta® (rebamapide). No pharmacological treatment is currently approved in Europe. In this article, I will provide updates on “new” pharmacological treatments—i.e., those beyond any approved as of January 2012, primarily those in clinical trials. Novel treatment for pharmacological management of dry eye disease is an area of active clinical development as evidenced by numerous recently completed or ongoing studies. The pharmacological agents in evaluation cover a wide range of putative mechanisms of action. However, firms developing these agents continue to be challenged by the limitations of animal models of efficacy, relatively small and variable clinical effects in Phase 2, and the investment in time and resources required for Phase 3.

Keywords Dry eye · Keratoconjunctivitis sicca · Regulatory agencies · Pharmacology

Introduction

The impact of dry eye disease on patient's health, visual function and quality of life may be substantial, as discussed in the Dry Eye Workshop (DEWS) in 2007 [1]. Like ocular

surface disease itself, management and therapy is complex and multifactorial. The Management and Therapy Subcommittee of DEWS recommended a staged, additive approach to management, depending upon the severity of the disease and the response to treatments. The categories of pharmacological treatments included artificial tear substitutes, gels and ointments (regulated by the U.S. FDA under the over-the-counter ophthalmic monograph, 21 CFR 349) [2, 3], anti-inflammatory agents (topical cyclosporine and corticosteroids and oral omega-3 fatty acids), secretagogues, serum, and systemic immunosuppressives [4•]. The regulatory issues in developing and approving ocular pharmacological treatments for dry eye was reviewed at a tear film and ocular surface (TFOS)/ Association for Research in Vision and Ophthalmology (ARVO) symposium. As of January 2012, the only approved pharmacological treatment in the U.S. or Canada is Restasis® (cyclosporine ophthalmic emulsion). In Japan, three products are approved: Hyalein® (hyaluronic acid), Diquas® (diquafasol), and Mucosta® (rebamapide). No pharmacological treatment is currently approved in Europe [5•].

In this article, I will provide updates on “new” pharmacological treatments—i.e., those beyond any approved as of January 2012, primarily those in clinical trials. This information is current as of 30 November 2012. I sought full papers on this topic in ophthalmology journals and MEDLINE. However, there seems to be a lag between conduct of these studies and full publication. Thus, I used the following additional sources:

- Internet based clinical trial registries: www.clinicaltrials.gov, www.clinicaltrialsregister.eu/, www.clinicaltrials.jp for the phrase “dry eye” or “sicca”. Note that the law and practice of clinical trial registration varies by country [6, 7].
- United States Patent database: (<http://www.uspto.gov/>) for patents issued between 1 January 2005 and 30

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November 2012 containing the words “dry eye” or “sicca” in the title. (Patents issued between 1 January 2002 and 31 December 2004 may be found in a previously published article) [8].

- Corporate press releases and presentations of which I am aware.

None of these sources is absolutely inclusive. While I have made best efforts to be thorough, it is possible that the above approaches missed some therapies. Also, sponsors do not always notify the public when a particular product is no longer under active development. Small companies in particular must raise funds frequently in order to pay the costs of development. There is one final caveat—the use of the clinical development phase is a continuum, not an absolute, and thus may not correctly and unambiguously describe the development stage [9].

Clinical Trial Registries

Clinicaltrials.gov (U.S. based) has 246 studies meeting the criteria of “dry eye” or “sicca” (135 of which are in the U.S., 27 are in China and 15 are in Japan). Of these 246 studies, 37 are currently “open” (meaning recruiting, not yet recruiting, or unknown). Further refining to those started in 2010 or later (my definition of “new”), and limiting to studies on pharmacological agents, there are 42. The European registry had 18 studies meeting the criteria, of which 6 met the further refinement. The Japanese registry had 12 studies meeting the criteria, of which 3 met the further refinement. There is some cross-registration of studies on different on-line registries, which is consistent with the guidances. Entries are not always current, and thus “conducting” versus “conducted” is a matter of judgment for the user. I used the organizational schema from the DEWS report [4•], with the category of “other” for those agents for which the mechanism of action or clinical effects are not yet well known.

Artificial Tears Substitutes

- Hyaluronic acid in various formulations continues to be evaluated by many firms including Alcon, River Plate, and Seikagaku (SI-614). This agent has the rare position of being regulated in the U.S. as a drug, a device, or an excipient, depending upon the product.

Anti-Inflammatory Agents

- Alcon conducted a Phase 2 study of Durezol® (difluprednate).

- Allergan evaluated a new formulation of cyclosporine.
- Bausch + Lomb conducted a Phase 2 study of BOL-303242-X Ophthalmic Suspension, a novel selective glucocorticoid receptor agonist (SEGRA) [10].
- EyeGate conducted two studies evaluating dexamethasone as applied by iontophoresis. They announced that they are now seeking other posterior segment indications.
- InSite Vision is planning a Phase 2 study of ISV-101 (bromfenac in DuraSite™ vehicle).
- ISTA (now part of Bausch + Lomb) conducted a Phase 3 study of bromfenac.
- Novagali has conducted a study of NOVA22007, a proprietary formulation of cyclosporine.
- Santen has conducted a Phase 2 study of DE-110 (a SEGRA).
- SARCode has completed several studies, including a Phase 3 study, of SAR 1118 (lifitegrast), an inhibitor of lymphocyte function-associated antigen (LFA-1) [11•, 12, 13] and has a safety trial ongoing. The firm announced plans for a second Phase 3 study.
- Sirion has completed a study of ST-603-005, a proprietary formulation of cyclosporine.
- The Wenzhou Medical College is conducting a study of two different non-steroidal anti-inflammatory agents and fluorometholone.

Secretagogues

- Otsuka and Acucela are co-developing rebamapide (OPC-12759). Several studies have been conducted, and it appears that there is a Phase 3 study ongoing in the U.S. and an additional safety study ongoing in Japan.
- Santen has conducted additional studies of diquafasol (DE-089).

Serum

- Chonman and Fundacion Imabis each conducted a study of autologous serum and umbilical cord serum.

Others

- Alcon conducted a study with ESBA105, an antibody fragment therapeutic with anti-tumor necrosis factor (TNF) activity, in the treatment of dry eye.
- Bitop is planning a study of Ectoin containing ophthalmic solution (a derivate of an amino acid found in extremophilic microorganisms).

Table 1 List of U.S. Patents issued between 1 January 2005 and 30 November 2012 containing the words “dry eye” or “sicca” in the title

US Patent number	Title	First author	Assignee	Date of issuance
6,872,382	Use of selective PDE IV inhibitors to treat dry eye disorders	Gamache	Alcon	29 March 2005
6,872,383	Use of macrolide compounds for the treatment of dry eye	Ueno	Sucampo	29 March 2005
6,874,884	Remedy for dry eye syndrome	Schwebel	–	3 April 2005
6,886,933	Remedy for dry eye syndrome	Schwebel	–	3 May 2005
6,887,858	Method of treating dry eye disease with purinergic receptor agonists	Yerxa	Inspire	3 May 2005
6,921,755	Method of treating dry eye disease with purinergic receptor agonists	Yerxa	Inspire	26 July 2005
7,026,296	Methods of treating dry eye disorders	Gamache	Alcon	11 April 2006
7,029,712	Treatment for dry eye syndrome	Thornton	–	18 April 2006
7,036,928	Remedy for dry eye syndrome	Schwebel	–	2 May 2006
7,060,728	11,12-Oxidoarachidonic acid derivatives and methods of their use in treating dry eye disorders	Belanger	Alcon	6 February 2004
7,063,857	Use of macrolide compounds for the treatment of dry eye	Ueno	Sucampo	20 June 2006
7,112,588	Use of proteasome inhibitors to treat dry eye disorders	Klimko	Alcon	26 September 2006
7,186,233	Dry eye treatment	Dohlman	Massachusetts Eye & Ear Infirmary	6 March 2007
7,189,697	Compositions and uses of a galectin for treatment of dry eye syndrome	Panjwani	Tufts College	13 March 2007
7,204,995	Treatment and control of dry eye by use of biodegradable polymer capsules	El-Sherif	–	17 April 2007
7,223,737	Method of treating dry eye disorders using glycosides	Ke	Alcon	29 May 2007
7,231,922	Apparatus, system and method for treating dry eye conditions and promoting healthy eyes	Davison	–	19 June 2007
7,235,556	Methods of treating dry eye disorders	Sharif	Alcon	26 June 2007
7,247,623	Method of treating dry eye disease with non-drying antihistamines	Yerxa	Inspire	24 July 2007
7,321,000	Ophthalmic composition containing N-acetyl-cysteine for the treatment of dry eye syndrome	Boldrini	Farmigea	22 January 2008
7,357,500	Remedy for dry eye syndrome	Schwebel	–	15 April 2008
7,381,707	Treatment of dry eye	Lin	Johnson & Johnson	3 June 2008
7,459,441	Remedies for dry eye and diseases associated with dry eye	Minagawa	Senju, Itoham Foods	2 December 2008
7,638,142	Therapeutic composition for the treatment of dry eye syndrome	Krawitz	Vitamin Science	29 December 2009
7,691,811	Transporter-enhanced corticosteroid activity and methods and compositions for treating dry eye	Bodor	–	6 April 2010
7,745,461	Method of treating dry eye disorders	Klimko	Alcon	29 June 2010
7,759,322	Method of treating dry eye disease with purinergic receptor agonists	Yerxa	Inspire	20 July 2010
7,825,102	Treatment of dry eye conditions	Fishman	Can-Fite	2 November 2012
7,897,642	Compositions and methods for dry eye syndrome	Dubow	–	1 March 2011
7,923,471	Method of treating dry eye disorders and uveitis	Klimko	Alcon	12 April 2012
8,114,420	Composition for treating dry eye and related methods of manufacture and methods of use	Xia	Bausch & Lomb	14 February 2012
8,207,226	Use of FAAH antagonists for treating dry eye and ocular pain	Gadd	Alcon	26 June 2012
8,211,434	KLK-13 antibody inhibitor for treating dry eye	Stern	Allergan	3 July 2012
8,211,942	Compositions and methods for dry eye syndrome	Dubow	–	3 July 2012
8,293,713	Beta-turn peptidomimetic cyclic compounds for treating dry eye	Cumberlidge	Mimetogen	23 October 2012
8,314,118	Methods and compositions for treating dry eye	Zagon	–	15 April 2012

- Can-Fite is conducting a Phase 3 study with oral CF101 (IB-MECA).
- CT Development (who acquired rights from Resolvix) is conducting a Phase 2 study of RX-10045 (a synthetic resolvin).
- Dong is conducting a Phase 2 study of DA-6034 eyedrops, a flavonoid derivative.
- Kissei completed a Phase 2 study of KLS-0611 and of KCT-0809 (ozagrel, a thromboxane A2 synthase inhibitor), and is planning additional studies of KCT-0809.
- Mimetogen conducted a Phase 2 study of MIM-D3, a growth factor mimetic.
- Novartis completed a study of AIN457 (secukinumab, a human anti-IL-17A monoclonal antibody) and ACZ885 (a fully human monoclonal antibody that inhibits IL-1 beta).
- Pfizer conducted early phase studies on tofacitinib (CP-690,550), a Janus kinase inhibitor, in patients in Japan and the U.S. [14].
- Rigel is planning a study of R-348 Ophthalmic Solution, a JAK-kinase inhibitor.
- Santen has conducted studies of DE-101, a topical ophthalmic suspension of rivoglitazone, a novel peroxisome proliferator-activated receptor (PPAR) gamma agonist used orally for the treatment of diabetes.
- Sylentis has completed a Phase 1 study of Drug: SYL1001, a form of interference RNA (RNAi) which inhibits the capsaicin receptor TrpV1.
- The Medical University of Vienna has completed a Phase 1 study of chitosan-N-acetylcysteine and is planning an additional study.
- The Medical University of Vienna is planning a study of a dietary supplement including Vitamin A.
- Thymosin Beta 4 was evaluated by RegeneRx in a completed study, and Michigan Cornea Consultants is currently conducting a study on this agent.
- Zea vision is conducting a study of a dietary supplement including Omega 3, Vitamins A, D3 and E.

Patents

Using the criteria, there were 36 patents that met the criteria for the approximate 7 years (Table 1). In a previous review of patents issued in the preceding 3 years, most (15/23) were assigned to Alcon, and three apparently covered products that were either marketed or in clinical development [8]. In this current period, 25 % (9/36) patents were assigned to Alcon, 11 % to Inspire, and 6 % to

Sucampo. As well, 31 % were to seemingly “independent” inventors. These patents also apparently cover at least one marketed product. An issued patent does not guarantee that the product named will be commercialized, or when or if it will be marketed. Patents may be either a leading or a trailing indicator of clinical development.

Other Sources

- Eleven Biotherapeutics is developing EBI-005, is a novel interleukin-1 (IL-1) receptor antagonist protein therapeutic for topical delivery to the eye for the treatment of ocular surface disease. An IND was filed in late 2012.
- Parion Sciences has evaluated novel topically applied epithelial sodium channel inhibitors on tear production in mice, suggesting that they have an interest in this area [15].

Conclusion

Novel treatment for pharmacological management of dry eye disease is an area of active clinical development as evidenced by numerous recently completed or ongoing studies. The multifactorial nature of the disease continues to result in multiple approaches to its management. The pharmacological agents in evaluation cover a wide range of putative mechanisms of action. Firms developing these agents continued to be challenged by the limitations of animal models of efficacy, relatively small and variable clinical effects in Phase 2, and the investment in time and resources required for Phase 3. With only a few ocular pharmacological agents approved worldwide, precedents are few and vary by country, requiring even larger and more complicated development plans to meet the worldwide need.

Disclosure G. Novack is a consultant for Acucela and Mimetogen, and serves as a consultant to numerous other pharmaceutical and medical device firms in the development of products.

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