Open-Angle Glaucoma: Drug Development Pipeline during the Last 20 Years (1995–2015)

André Vicente^{a, b} Sylvie Prud'homme^d Joana Ferreira^{b, c} Luís Abegão Pinto^b
Ingeborg Stalmans^d

^aOphthalmology, Department of Clinical Sciences, Umeå University, Umeå, Sweden; ^bVisual Sciences Study Center, Faculty of Medicine, Lisbon University, and ^cDepartment of Ophthalmology, Centro Hospitalar Lisboa Central, Lisbon, Portugal; ^dDepartment of Ophthalmology, University Hospitals Leuven, Leuven, Belgium

Key Words

Open-angle glaucoma · Drug development · International Clinical Trials Registry Platform

Abstract

Objectives: To analyse drug development for open-angle glaucoma during the last 20 years. **Methods:** Research was performed by referring to clinical trials registered at the International Clinical Trials Registry Platform (ICTRP). A search for the condition “open-angle glaucoma” with the intervention “drug” was performed. We included trials registered from 01/01/1995 to 01/01/2015, only involving studies in phases 1, 2, and 3. Only studies resorting to novel treatment strategies (either novel drugs or yet-untested fixed associations of approved medication) were considered. **Results:** We recorded 158 studies for the condition of open-angle glaucoma with a drug-based intervention; 65 of the studies reported phase 2 trials and 74 reported phase 3 trials. Pharmaceutical companies were the primary sponsors of 95.3% of the trials. Most of the studies (66.5%, $n = 105$) involved a new drug, and the remainder (33.5%, $n = 53$) tested fixed

drug associations. The bulk of the trials ($n = 99$, 62.7%) involved the use of prostaglandin analogues, either as a comparator or a study drug. In descending order of frequency, the studies conducted involved Rho-kinase inhibitors ($n = 15$), carbonic anhydrase inhibitors ($n = 14$), β -blockers ($n = 7$), angiostatic steroids ($n = 6$), α_2 -adrenergic agonists ($n = 4$), 5-HT_{2A} receptor agonists ($n = 4$), and NMDA receptor antagonists ($n = 2$). A cyclin-dependent kinase inhibitor, an LIM-domain kinase 2 inhibitor, an A1 adenosine receptor agonist, catechin, macrolide, saffron, and seawater were each tested in 1 clinical trial. **Conclusion:** Research into the medical treatment of glaucoma indicates the use of prostaglandin analogues. However, there are a significant number of trials testing other drug classes, particularly Rho-kinase inhibitors. This new focus could lead to a potential increase in the number of therapeutical options for the management of glaucoma in the future.

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A.V. and S.P. contributed equally to this paper and should be considered first co-authors.

Introduction

Glaucoma is one of the most prominent causes of irreversible blindness in the world, with a global prevalence of 3.45% among people 40–80 years of age. It is estimated that approximately 111.8 million people will have glaucoma by 2040 [1]. The modifiable risk factor for glaucoma is high intraocular pressure (IOP). The compression of this ocular parameter continues to be the mainstay of glaucoma treatment, either requiring medical treatment (usually topical instillation of IOP-lowering agents) or surgery [2].

Glaucoma medical treatment has evolved in the last few decades from IOP modulators (such as pilocarpine and timolol) to myriad new drugs that seek to exploit new treatment paradigms [3]. Some of the limitations related to the existing IOP-lowering therapies include harmful side effects, a significant proportion of non-responders, and the need for combination therapy to achieve target IOP [4].

Accordingly, there is an unmet need that has driven research into new combination therapies and novel treatment paradigms. Moreover, as IOP represents one risk factor but does not explain the entire pathophysiology of the disease [5], investment into research of glaucoma drugs that function through other mechanisms is now occurring. Some of the more recent approaches include molecules that influence ocular haemodynamics and neuroprotective agents [6].

The translation of novel therapies from bench to bedside is a protracted process, involving multiple phases before the promising drug candidates reach the clinic [7, 8]. The purpose of this study is to provide an overview of the clinical trials registered for the treatment of primary open-angle glaucoma with novel drug candidates over the last 20 years as well as a view to identify emerging trends in the field.

Methods

A systematic search of the International Clinical Trials Registry Platform (ICTRP) was performed. This platform was established in 2006 by the World Health Organization, with the objective of disclosing information about all the clinical trials that involve human beings. Thus, the platform requires publication of an internationally agreed-upon set of information about the design, conduct, and administration of clinical trials [9]. The ICTRP database includes registrations from ClinicalTrials.gov and the European Union (EU) Clinical Trial Register, among others.

A query was performed according to the optimized search protocols in this database [10]. Accordingly, the search for the condition “open-angle glaucoma” with the intervention “drug” was performed. The interval for the registration of research was from 01/01/1995 to 01/01/2015. Only studies on phase 1, 2, and 3 trials were included. There were no restrictions on the recruitment status

Table 1. Overview of drug-related clinical trials in open-angle glaucoma in 1995–2015

Year registered	Phase 1	Phase 2	Phase 3	Phases 1 + 2	Phases 2 + 3	Total
1995	0	0	3	0	0	3
1996	0	0	2	0	0	2
1997	0	0	1	0	0	1
1998	0	1	0	0	0	1
1999	0	1	1	0	1	3
2000	0	0	2	0	0	2
2001	0	0	5	0	0	5
2002	0	1	1	0	0	2
2003	0	2	2	0	0	4
2004	0	1	3	0	0	4
2005	0	2	7	0	0	9
2006	0	4	3	1	0	8
2007	1	9	2	0	0	12
2008	0	8	5	1	2	16
2009	0	7	6	1	0	14
2010	1	4	9	1	0	15
2011	1	7	12	2	0	22
2012	1	7	1	2	0	11
2013	1	7	3	0	0	11
2014	0	4	6	3	0	13
Total	5 (3.2%)	65 (41.1%)	74 (46.8%)	11 (7.0%)	3 (1.9%)	158

or the countries involved. All trials regarding already-approved medication were excluded. An exception was made when a trial compared an approved medication with a new agent, or when a new agent was being used in combination with an approved medication.

The following parameters were recorded from each of the trials: trial ID, date of last update on trial status, public title, scientific title, acronym, primary and secondary sponsor, date of registration, source register, recruitment status, minimum and maximum age for inclusion, gender inclusion, exclusion and inclusion criteria, date of enrolment, target size, study type, phase, study design, countries involved, conditions, interventions, and primary and secondary outcomes. The mechanism of action for each compound was determined by evaluating the published literature. Only the main component was considered in the case of fixed associations. For drugs with >1 suggested mechanism, classification was performed by considering the primary mode of action.

All descriptive statistical analysis was performed using SPSS v18.0 (IBM Corp., Armonk, NY, USA).

Results

The query provided 158 entries registered between 01/01/1995 and 01/01/2015. Of these, only 4 had been directly registered in the ICTRP. One hundred and fifty-three were initially submitted to ClinicalTrials.gov ($n =$

Fig. 1. Overview of the drug-related clinical trials in open-angle glaucoma during the 1995–2015 period.

149) and 5 to the EU-related database. Nearly the entire set of entries had been registered by the pharmaceutical industry ($n = 150$).

The vast majority of entries involved phase 2 and 3 trials (65 [41.1%] and 74 [46.8%], respectively), with only 5 studies in the earliest phase. A significant number of trials (14 [8.9%]) covered more than a single phase (i.e., either phases 1 + 2 or phases 2 + 3), and these were categorized separately (Fig. 1; Table 1). In 66.5% ($n = 105$) of the trials, a single new drug was being tested. In 33.5% ($n = 53$) of the identified trials, fixed associations of drugs were being tested, and only 24.5% ($n = 13$) of these were associated with a new drug. Only 5.1% ($n = 8$) of the selected clinical trials were still actively recruiting patients.

There was missing data in the ICTRP database for 22.2% ($n = 35$) of the registered clinical trials. Phase 1 clinical trials lacked information in 20% ($n = 1$), phase 2 in 16.9% ($n = 11$), and phase 3 in 31.1% ($n = 23$) of the registered trials.

Geographical analysis was possible in all but 12 studies. Out of these 146 studies, the majority (64.3%) were performed in the USA. EU countries accounted for almost 15% of the total of study locations, and the remaining 20% were conducted elsewhere (Fig. 2).

Information on the target size sample was available in 88.0% ($n = 139$) of the trials, with a large heterogeneity between studies (mean $\pm$ SD, 246.2 ± 264.2). The minimum recruitment age was available in 93.7% ($n = 148$) of the studies, whereas the maximum age was registered in only 21 trials and was, on average, 76.6 ± 11.1 years. Only 1 trial included children <18 years (0.6%, $n = 1$). All the analysed clinical trials included both males and females.

Fig. 2. Distribution of the clinical trials by region.

The descriptive analysis of the different mechanisms of action for the test drugs is detailed in Table 2. IOP modulation was the most common mechanism of action of the drugs in the clinical trials (87.2%, $n = 138$). Drugs that combine IOP modulation and neuroprotection were tested in 10.1% of the trials ($n = 16$); drugs that function by enhancing neuroprotection were tested in 1.9% ($n = 3$). Prostaglandin analogues were the drugs tested in the majority of the trials (62.7%, $n = 99$), most of which were phase 3 trials ($n = 57$). The Rho-kinase inhibitors ranked second (9.5%, $n = 15$), with carbonic-anhydrase inhibi-

Table 2. Mechanisms of action and different classes of drugs in the clinical trials researched

	Phase 1	Phase 2	Phase 3	Phases 1 + 2	Phases 2 + 3	Total
IOP modulation						
Prostaglandin analogues	4	34	57	4	0	99 (62.7%)
Carbonic anhydrase inhibitors	0	3	10	0	1	14 (8.9%)
β -Blockers	0	4	2	1	0	7 (4.4%)
Angiostatic steroids	0	4	0	0	2	6 (3.8%)
α_2 -Adrenergic agonist	0	2	1	1	0	4 (2.5%)
5-HT _{2A} receptor agonists	0	4	0	0	0	4 (2.5%)
Cyclin-dependent kinase inhibitors	0	1	0	0	0	1 (0.6%)
LIM-domain kinase 2 inhibitor	0	0	0	1	0	1 (0.6%)
A1 adenosine receptor agonists	0	1	0	0	0	1 (0.6%)
Macrolide	1	0	0	0	0	1 (0.6%)
Subtotal	5	53	70	7	3	138 (87.2%)
Neuroprotection						
NMDA receptor antagonists	0	0	2	0	0	2 (1.3%)
Catechin	0	0	0	1	0	1 (0.6%)
Subtotal	0	0	2	1	0	3 (1.9%)
IOP modulation + neuroprotection						
Rho-kinase inhibitors	0	11	2	2	0	15 (9.5%)
Saffron	0	1	0	0	0	1 (0.6%)
Subtotal	0	12	2	2	0	16 (10.1%)
Seawater	0	0	0	1	0	1 (0.6%)
Total	5 (3.2%)	65 (41.1%)	75 (47.5%)	11 (7.0%)	3 (1.9%)	158 (100%)

tors and β -blockers being tested in 8.9% ($n = 14$) and 4.4% ($n = 7$) of the trials, respectively. Other studied medications included angiostatic steroids ($n = 6$), α_2 -adrenergic agonists ($n = 4$), 5-HT_{2A} ($n = 4$), and NMDA receptor antagonists ($n = 2$).

Discussion

Investigations into medical treatments for glaucoma have shown compelling advances in the last 2 decades. This mostly US-based, industry-related research has produced a number of commercially available alternatives ranging from new drugs to sophisticated administration systems (such as fixed combinations). Clinical trials require costly and complex bureaucratic investments and infrastructure; therefore, they tend to be financed by companies from North America, Western Europe, and East Asia [11]. The high percentage of clinical trials performed in the USA might be explained by health care access inequality, inadequacy, and poverty, as low-income minority males tend to be disproportionally recruited;

these trials can be important income providers for subjects [12]. Another possible reason for US- or EU-centred trials could be that the regulatory bodies from these high-income markets (i.e., the FDA and EMA) require trials to be performed in certified centres in their own countries or regions.

In addition to IOP-lowering potency, drug clinical trials are also used to determine safety profiles, specific target populations, different drug concentrations, and even fixed associations. For instance, the high number of studies on prostaglandin analogues refers to the interest that this class of drugs has created, along with trials testing these molecules involving issues such as preservative-free formulations, different regimens, and whether their effect can be maximized by associating them with a second drug class (such as a β -blocker) in a fixed combination [13]. This last point is particularly important, as the majority of glaucoma patients are not sufficiently controlled with a single drug [14]. As a result, double, triple, or even quadruple therapy is required to achieve the IOP target. However, even if tolerated initially, long-term complex multi-therapy does have its disadvantages. In this case,

research into fixed-combination therapy is based on a number of potential advantages, including reduced exposure to preservatives, a reduced risk of preservative-related ocular surface disease symptoms, the elimination of washout associated with insufficient time separation of instillations, and reduced numbers of total instillations [15]. Furthermore, due to simplification of the instillation regimen, fixed combinations may improve treatment adherence and persistence. Therefore, fixed combinations enhance the stability of IOP control over time [16–18].

The toxic effects of preservatives are dose dependent and cumulative. These substances tend to be responsible for disease of the ocular surface and have also been associated with increased intraocular inflammation after surgery [19, 20]. The development of clinical trials for preservative-free glaucoma drug formulations is also important for the evaluation of the possible pharmacokinetic differences [21].

The mechanism of action of the majority of glaucoma drugs tested in the registered trials was IOP modulation. An actin-related agent tested in these trials was latrunculin B. This agent is a macrolide that originated from a sponge from the Red Sea (*Latrunculia*). It inhibits the assembly of actin microfilaments by binding to free actin monomers in the cytoplasm, inducing cellular relaxation and weaker contacts between the cells and the matrix [22]. In a smooth-muscle-independent pathway, trabedononon is a highly selective adenosine receptor agonist that improves flow by upregulating various proteases that remove accumulated proteins that can impair trabecular flow [23]. Angiostatic steroids have also been tested as possible IOP-lowering molecules for this disease. One of the tested molecules was anecortave acetate, which is a synthetic molecule derived from cortisol [24]. The 5-hydroxy-tryptamine (5HT_{2A}) agonists have also been evaluated as IOP-lowering agents in some clinical trials ($n = 4$). They represent a new mechanism of action [25], which is also the case with cyclin-dependent kinase (CDK) inhibitors [14] and LIM-domain kinase 2 inhibitors. The latter is a kinase associated with the regulation of the IOP, and its inhibition enhances fluid trabecular outflow.

Neuroprotection represents an emerging therapeutic approach for the treatment of primary open-angle glaucoma. Saving retinal ganglion cells and repairing damaged neurons could therefore be achieved not only by decreasing IOP but also by avoiding ischaemia, oxidative stress, excitotoxicity, defective axonal transport, trophic factor withdrawal, and neuroinflammation [3]. NMDA receptor antagonists, such as memantine, were tested in 1.3% of the clinical trials. Decreasing excitotoxicity is the

mechanism of action, by reducing the excessive amounts of glutamate. A catechin (epigallocatechin-gallate) was also investigated as a neuroprotective agent. This is a powerful antioxidant with a proposed effect on the inner retinal function in eyes with early-to-moderate glaucomatous damage [26].

Some of the drugs tested in the clinical trials were able to combine mechanisms of action, modulate IOP, and provide neuroprotection. Interestingly, there appears to be an active interest in trabecular meshwork-acting drugs. Of these, Rho-kinase inhibitors are currently the most studied, with 11 trials in phase 2. These agents relax the trabecular meshwork by inhibiting the actin of the contractile smooth muscle of the cytoskeleton, increasing the trabecular aqueous outflow [27]. In addition, these agents are progressively being recognized to have neuroprotective activity [28].

Two clinical trials with more particular approaches were also defined. A clinical trial from Iran on the use of saffron as an IOP-lowering agent was registered. Saffron has high concentrations of 2 carotenoid-related components, crocin and crocetin, with antioxidant properties [29]. The role of oxidative stress in primary open-angle glaucoma has been documented [30, 31]. The trabecular matrix is sensitive to oxidative stress, and disturbed cell homeostasis in this tissue may cause structural changes that impair aqueous humour outflow and lead to an IOP increase. The antioxidant neuroprotective properties may also help in preventing glaucomatous optic neuropathy [32]. Microglial activation in the early stages has been shown to be an indicator of neurodegeneration severity in glaucoma. A recently published study has investigated the role of crocin in the inhibition of lipopolysaccharide-induced microglial activation, and determined that crocin effectively suppresses microglial activation and NF- κ B/YY1 signalling, inducing an upregulation of CX3CR1 expression [33].

A clinical trial with the aim of studying the combined use of seawater and magnetic therapy is currently registered in the USA. However, no scientific rationale for this intervention is provided.

An important observation was the increase in the number of phase 1 trials that were registered when comparing the first decade evaluated with the second (from 0 trials in 1995–2005 to 5 in 2006–2015). This pattern is also reflected in the growing rate of registered phase 2 and 3 trials. The implementation of laws regulating the necessity of and improvements in clinical trial registration might be responsible for the apparent growth in the number of glaucoma trials [34]. Furthermore, even in the re-

gions where clinical trials are regulated and compulsory, laws tend to exclude all trial types, e.g., phase 1 trials and device trials. This can lead to a limitation in the number of phase 1 trials that are registered [35].

One key aspect of this query is that it demonstrated a certain proportion of the studies registered at these official platforms did not provide all the required information. This is important, as lack of information could undermine the scrutiny of ongoing trials, as required by the Declaration of Helsinki. In principle, no missing data should occur in queries like ours, as any lack of data potentially limits interpretation. Since the International Committee of Medical Journal Editors (ICMJE) determined in 2005 that clinical trials being considered for publication must be registered in publicly accessible registries, the number of registrations and the standards of data registration have increased [7, 8].

Conclusion

The medical treatment of glaucoma is an evolving field focused on strategies that include developing new drugs and optimizing existing therapies by testing fixed associations. While the last 2 decades have made prostaglandin analogues one of the first-line treatments in this field, there is also a large investment in novel compounds such as Rho-kinase inhibitors. Despite the small number of phase 1 trial registrations, the large number of trials currently in phase 3 could represent a broadening of medical options for glaucoma management in the near future.

Disclosure Statement

We have no conflicts of interest to disclose.

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