Intraocular pressure efficacy of glaucoma medications versus placebo in phase II compared to later phase trials

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ABSTRACT

This review aimed to compare the predictive value between the untreated reduction in intraocular pressure (IOP) from baseline or placebo measured in early phase clinical trials to phase III and IV results for glaucoma medicines. Published, placebo-controlled, randomised, parallel, single-masked or double-masked clinical trials with at least one phase II, III and IV study available were reviewed. This study included 50 articles evaluating 9 medicines from 59 active arms and 18 placebo arms. For all studies the phase II IOP reduction from placebo showed less decrease compared to the decrease from baseline ($p<0.04$). For all medicines, reductions from morning baseline in phase II did not predict better than the decrease from placebo for phase III ($p=0.15$) or IV ($p=0.08$) reductions in IOP. In contrast, diurnal IOP reduction from baseline in phase II predicted decreases better than placebo in phase III ($p=0.007$) and IV ($p=0.02$). Generally, for prostaglandins, β blockers and carbonic anhydrase inhibitors for the morning trough and diurnal curve there was no difference in pressure reduction from baseline for phase II compared to phase III or IV ($p\geq0.23$). In contrast, where comparisons were available for the decrease in pressure from placebo there were differences for phase II compared to phase III and phase IV ($p\leq0.02$). This study suggests that in early phase glaucoma trials, using the reduction from untreated baseline in general better approximates the results of later regulatory and post-commercialisation trials than the decrease from placebo.

INTRODUCTION

To gain regulatory approval for a new medicine a pharmaceutical company must take the new product through a series of clinical trials (phases I–III). A phase I trial represents the first instance a new product is used in human subjects and is performed primarily to collect safety information. In a phase II trial a new product is used for the first time in patients with the target disease to gain dosing and concentration information. At least two phase III trials are performed, and they are expanded in size and duration. These trials typically provide the most information on the efficacy and safety for the new product on which regulatory approval is based. Phase IV studies are those which are performed after commercial release of the medicine.

A pharmaceutical company must make a decision at the end of each phase whether the efficacy and safety information warrants the resources, in money and personnel, to continue clinical development. Consequently, adequately performed early phase trials should predict the results of phase III and IV studies. However, the limited size and duration, as well as the subject selection, might restrict the ability of early phase trials to accurately predict future results.

We showed in a previous paper that the percentage reduction of intraocular pressure (IOP) from untreated baseline in phase I and II generally approximated efficacy in phase III and IV[1] for current glaucoma medicine classes including prostaglandins, β blockers, topical carbonic anhydrase inhibitors and α agonists. However, early phase trials are often controlled by placebo, which are often thought to give more accurate comparison to efficacy because they account for any unattended placebo effect in the active controlled measurements.

The purpose of this study was to evaluate the predictive value of early phase trials for ocular hypotensive efficacy with glaucoma medicines in phase III and IV trials between the untreated reduction from active baseline and placebo.

MATERIALS AND METHODS

Study criteria

Using published literature found on PubMed (http://www.ncbi.nlm.nih.gov/entrez/query) and medical reviews on the US Federal Drug Administration's drug approval website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm), we included in this study phase I and II trials for glaucoma medicines that became commercially available after 1977 that had a placebo arm and involved patients with glaucoma. These medicines were chosen as they are ones available generally for prescription to patients with glaucoma in the current market (table 1). The following search terms were used: primary open-angle glaucoma, ocular hypertension, IOP, diurnal, monotherapy, baseline, reduction, β blockers (timolol, timolol gel forming solution, betaxolol, carteolol, levobunolol), carbonic anhydrase inhibitors (dorzolamide, brinzolamide), α agonists (brimonidine, brimonidine preserved with polyquaternium 1, brimonidine preserved with chlorine dioxide, apraclonidine), prostaglandins (latanoprost, travoprost, bimatoprost) and combination treatment (brinzolamide/timolol, dorzolamide/timolol, latanoprost/timolol, travoprost/timolol, brimonidine/timolol, bimatoprost/timolol). Brand names of single and fixed combination agents were also used as search terms.

For phases I–III we used the first four available studies under each phase and to limit the data collection, and for consistency, the first three available phase IV clinical trials for that same medicine were

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Table 1 Percentage decrease from baseline and from placebo at the morning trough at the end of treatment periods

			Phase II			Phase III		Phase IV	
Medicine	Concentration(s)	Dosing (times per day)	N	Percentage decrease from baseline	Percentage decrease from placebo	N	Percentage decrease from baseline	N	Percentage decrease from baseline
Betaxolol	0.25%	2	1	13.2	11.5	1	13.8	1	13.3
Bimatoprost	0.03%	1, 2	4	31.1	22.6	2	33.8	2	32.1
Brimonidine	0.2%	2	1	18.3	12.0	3	14.4	2	17.9
Brinzolamide	1%	2, 3	1	17.0	13.0	3	16.0	0	NA
Dorzolamide	2%	2, 3	3	20.1	13.9	2	14.6	2	16.8
Latanoprost	0.005%, 0.006%	1, 2	2	29.8	24.8	3	31.9	3	29.5
Levobunolol	0.5%, 0.6%	1, 2	3	20.5	11.8	4	23.5	2	23.8
Timolol	0.5%	1, 2	1	39.6	30.6	3	29.2	1	21.8
Travoprost	0.004%	1	1	31.4	21.7	3	27.9	3	30.9
Mean decrease			17	25.0	17.9	24	23.5	16	24.8
Comparison with phase II reduction from baseline						p=0.58		p=0.97	
Comparison with phase II reduction from placebo						p=0.04		p=0.02	

A one-way analysis of variance (ANOVA) test was used for p values. The p values show whether there is a statistically significant difference between the phase II data compared to phase III and phase IV. Decrease from baseline/placebo was determined by the average decrease per study.
N, number of treatment arms.

included. Nonetheless, studies were not available at all for some phases for some medicines. The primary goal was to determine the predictive value of early phase trials (phase II) with the ocular hypotensive efficacy observed in later phases (III and IV).

Only prospective, parallel, single-masked or double-masked clinical trials were included. Crossover and open-label studies were excluded. We excluded early studies that did not have a placebo comparison or reported neither a 3-point diurnal curve nor morning trough. Studies with a concentration difference greater than ±25% of the concentration that become commercially available were excluded. We also excluded medicines for which we could find no published phase II articles or those shorter than 24 h of treatment. Studies that did not state at which time the pressure measurements were taken were also excluded. If a study provided diurnal and trough measurements on the last active treatment day but did not provide the appropriate baseline for one of those measurements, we included only the one with the proper baseline.

Procedures

Morning trough and diurnal curve IOP values were extracted from articles meeting the study criteria and entered into an Excel spreadsheet (Microsoft, Redmond, Washington, USA) for each treatment's baseline and last day of treatment. For each article, we evaluated the reduction in the pressure from baseline to the last active treatment day for the placebo (in early studies) and for the active compound. Depending on what data a particular study provided, we analysed the pressure reductions at the morning trough, or the diurnal curve (all three or more time points averaged together), or both.

Quality assurance was performed on 10% of the entries, in which a separate Excel spreadsheet was created and compared to the original to assure there were no mistakes. Results of the quality assurance analysis showed no data entry errors.

Statistics

PRN Pharmaceutical Research Network, LLC (Cheyenne, Wyoming, USA) analysed the data. The level to declare significance difference between any groups being analysed was 0.05 and all analyses were two way. The differences in percentage reduction from untreated baseline and placebo in phase II to the reductions in phase III and IV were analysed with a one-way analysis of variance (ANOVA) as is consistent for continuous data.[2] The differences among classes of medicines whether percentage reduction from baseline or placebo was best was analysed by a χ^2 test or Fisher (2×2 table with one value 5 or less) as typical for qualitative data.[2] For this test all classes and study averages were combined into one mean value.

RESULTS

This study originally reviewed 116 articles, but of these, 65 were excluded because they did not meet all inclusion criteria. Most commonly the excluded articles had a crossover design, no placebo arm or unclear IOP measurement times. A total of 9 medicines from 50 articles were evaluated in this study with 59 treatment arms and 18 placebo arms: betaxolol,[3–6] bimatoprost,[7–14] brimonidine,[5 15–19] brinzolamide,[20–23] dorzolamide,[24–30] latanoprost,[7 8 31–36] levobunolol,[37–45] timolol,[30 34 35 46 47] and travoprost.[8 48–53]

The morning trough results are shown in table 1 and diurnal results in table 2. There were 57 morning trough treatment arms and 36 diurnal treatment arms. There were 35 treatment arms that had morning trough and diurnal data. There was no difference in mean pressure reduction from baseline (all studies together) for phase II for the morning trough compared to phase III and IV separately (p=0.58 and p=0.97, respectively) or for the diurnal pressure (p=0.20 and p=0.26, respectively). In contrast, the phase II reduction in pressure from placebo showed differences compared to phase III and IV for the morning trough (p=0.04 and p=0.02, respectively) and also for the diurnal curve (p=0.0008 and p=0.002, respectively).

Table 3 shows the number of phase III or IV studies which either the average phase II reduction of pressure from baseline or placebo best approximated phase III or IV results. The reduction from baseline in phase II for the morning trough was not better than the decrease from placebo for predicting phase III (p=0.15) or IV (p=0.08). In contrast, the diurnal pressure reduction from baseline in phase II was better than from placebo for predicting decreases in phase III (p=0.007) and IV (p=0.02).

Table 2 Active compound percentage decreases from baseline and from placebo over the diurnal curve at the end of treatment periods

	Phase II			Phase III		Phase IV	
	N	Percentage decrease from baseline	Percentage decrease from placebo	N	Percentage decrease from baseline	N	Percentage decrease from baseline
Betaxolol	1	27.5	14.8	0	NA	0	NA
Bimatoprost	4	26.3	21.1	2	30.8	2	30.0
Brimonidine	1	20.6	15.1	0	NA	0	NA
Brinzolamide	1	17.4	12.0	2	18.8	0	NA
Dorzolamide	3	18.4	15.7	1	20.0	1	18.3
Latanoprost	1	35.9	29.2	3	31.9	3	27.1
Levobunolol	0	NA	NA	0	NA	0	NA
Timolol	0	NA	NA	3	27.8	1	20.9
Travoprost	1	30.0	21.6	3	28.0	3	29.9
Mean decrease	12	24.3	18.7	14	27.3	10	27.0
Comparison with phase II reduction from baseline				p=0.20		p=0.26	
Comparison with phase II reduction from placebo				p=0.0008		p=0.002	

A one-way analysis of variance (ANOVA) test was used for p values. The p values show whether there is a statistically significant difference between the phase II data compared to phase III and phase IV. Decrease from baseline/placebo was determined by the average decrease per study.
N, number of treatment arms.

Table 4 demonstrates data from specific drug classes. Where comparisons were available, for prostaglandins, β blockers and carbonic anhydrase inhibitors for the morning trough and diurnal curve there was no difference in pressure reduction from baseline for phase II compared to phase III or IV ($p \geq 0.23$). In contrast, where comparisons were available for the decrease in pressure from placebo there were differences for phase II compared to phase III and phase IV ($p \leq 0.02$). Further, the decrease in pressure from placebo was less than the decrease from baseline in phase II itself for prostaglandins ($p < 0.001$) and carbonic anhydrase inhibitors ($p = 0.01$).

DISCUSSION

The results of this review indicated that the reduction from untreated baseline of the active medicine typically better approximated the results of later regulatory studies and post-commercialisation trials than does the decrease from placebo, and that this applied for the morning and diurnal pressures. Further, no apparent divergences of this basic finding exist for specific medicine classes, except for brimonidine, where too few studies were available to make a useful estimate of this class. However, caution is warranted in applying these findings clinically because results deviated among individual studies. The results are consistent, however, to our prior results that demonstrated that the reduction from baseline in phase II approximated the results in later phase trials.[1] In total, for phase II approximately 30% of the drug efficacy may have resulted from the placebo effect (table 1).

The reason why the phase II reduction from baseline generally better approximated later phase studies than placebo is not completely clear from these results. Placebo arms are not typically included in glaucoma phase III and IV studies for ethical reasons. Accordingly, the basis for which medicines are judged by regulatory personnel and clinicians for later stage studies is generally from reduction from baseline compared to an active control. Therefore, it makes sense that in early phase studies a reduction from baseline may better approximate an IOP decrease for later studies than does placebo.

However, placebo arms remain important in early phase studies to confirm that a new medicine has a real clinical effect because it helps eliminate potential causes of bias when assessing within group comparisons such as: regression to the mean, spontaneous improvement of disease, the effect of additional treatments unknown to the investigator as well as patient conditioning and behavioural effects.[54–57]

Nonetheless, the results of this review should give a pharmaceutical company, investors and clinical investigators some confidence that a glaucoma medicine that is effective in early

Table 3 Ability of phase II reduction of intraocular pressure, from baseline or placebo, to predict phase III or IV for diurnal and morning trough intraocular pressure for all medicines combined

Reduction from baseline	Percentage reduction (%)	Phase II reduction from baseline predicted better phase III or IV results (N)	Phase II reduction from placebo predicted better phase III or IV results (N)	Total N	Value
Morning trough					
Phase III	24.6	15	9	24	0.15
Phase IV	18.0	11	5	16	0.08
Diurnal					
Phase III	25.2	11	3	14	0.007
Phase IV	18.5	8	2	10	0.02

A Fisher test was used for all p values except a χ^2 test was used with phase III trough because it did not have a value of 5 or less.
N, number of treatment arms.

Table 4 Average absolute percentage differences between phase II reduction from baseline (then placebo) and each phase III and IV study (%)

	Prostaglandin		Carbonic anhydrase inhibitor		β blocker	
	% Average	p Value	% Average	p Value	% Average	p Value
Morning trough						
Phase II active to phase II placebo		<0.001		0.01		0.10
Phase II from baseline versus phase III	3.3	0.94	3.6	0.23	6.2	0.90
Phase II from placebo versus phase III	7.8	<0.001	2.4	0.008	8.0	<0.001
Phase II from baseline versus phase IV	1.9	0.97	3.4	0.65	8.2	0.83
Phase II from placebo versus phase IV	7.7	<0.001	2.9	0.02	11.0	0.003
Diurnal						
Phase II active to phase II placebo		<0.001		0.0002		
Phase II from baseline versus phase III	3.6	0.43	1.6	0.60		
Phase II from placebo versus phase III	6.3	<0.001	5.9	0.0002		
Phase II from baseline versus phase IV	4.6	0.87	0.1	NA		
Phase II from placebo versus phase IV	6.2	<0.001	2.5	NA		

NA, could not perform statistical analysis since there was only one study.

regulatory trials, especially in the reduction from baseline, may have similar efficacy in phase III and after commercialisation.[1]

This study suggests that in early phase glaucoma trials using the reduction from untreated baseline in general better approximates, than the decrease from placebo, the results of later regulatory and post-commercialisation trials.

However, the results of this study are limited in that it reviewed only products launched commercially. Similar data and the predictive values of their regulatory trials generally are not available for the products that failed development. More research is needed, in general, with clinical measures and the development process, to help investigators and pharmaceutical companies know how to most efficiently develop a new glaucoma product.

Contributors RAS: acquisition of data, analysis of data. LAN: acquisition of data, analysis of data, revising the article. JAS: conception and design, revising the article, final approval. WCS: conception and design, interpretation of data, drafting/revising the article, final approval.

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