Brimonidine (Alphagan®): A clinical profile four years after launch

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ABSTRACT. *The early information on the clinical efficacy, safety, and tolerability of brimonidine 0.2% were obtained from studies that compared brimonidine monotherapy with timolol and betaxolol. These studies showed its intra-ocular pressure lowering efficacy to be comparable with timolol and superior to betaxolol. The data from the timolol studies showed consistent results after four years. These findings have been confirmed by additional studies in the clinical setting.*

More recently, several clinical trials have been completed investigating the role of brimonidine as adjunctive medication to beta-blockers and as replacement therapy to other intraocular pressure lowering compounds. When added to beta-blockers, brimonidine is superior to dorzolamide, similar in efficacy but better tolerated than pilocarpine, and more predictable than latanoprost.

Data from replacement studies have indicated that there may be advantages in replacing rather than adding medications in the treatment of glaucoma. Eur J Ophthalmol 2001; 11 (Suppl 2): S72-S77

KEY WORDS. *Brimonidine, Clinical trials, Glaucoma*

INTRODUCTION

Brimonidine tartrate 0.2% (Alphagan®; Allergan, Inc.) is becoming increasingly popular for the initial and long-term management of ocular hypertension and glaucoma. It has been studied in more than 2000 patients in clinical trials and, since its introduction in 1996, more than 30 million units have been dispensed. Based on this experience, we now have extensive information about this compound.

In initial clinical studies, brimonidine monotherapy was compared with the beta-blockers timolol (1-4) and betaxolol (5). This report provides an update on the extension of one of the long-term studies that compared brimonidine with timolol. Results from additional clinical trials of various designs are also presented, to highlight the use that brimonidine may have in glaucoma therapy as monotherapy, adjunctive, or replacement medication.

Long-term studies comparing brimonidine and beta-blocker monotherapy

A subgroup of patients from 7 sites of one of the long-term studies comparing brimonidine 0.2% to timolol 0.5%, both administered twice daily, continued beyond the 1-year protocol (3) through years 3 and 4.

Three-year results

By year 3 brimonidine provided sustained, or even improved, intraocular pressure (IOP) reduction at trough, compared with timolol 12 hours after instillation (Fig. 1) (6). This means that with longer-term use, the slight advantage reported for timolol over brimonidine at the trough IOP measurement (Fig. 1), as reported in the 1 year studies (1-4), was no longer present. During Year 3, brimonidine reduced mean IOP from baseline by 5.02 mmHg compared with 5.57 mmHg with tim-

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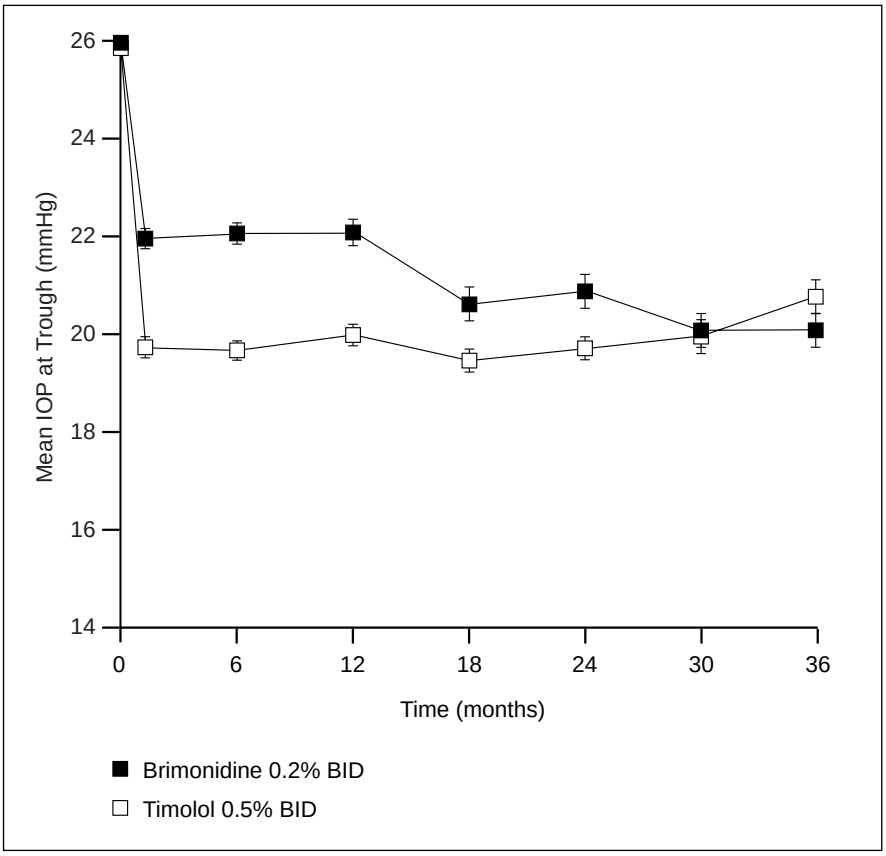

Fig. 1 - *Trough IOP throughout 36 months of follow-up (6).*

olol (p = 0.383). Using 95% confidence intervals with equivalence defined as within 2 mmHg, the reductions produced by brimonidine were equivalent to those produced with timolol after 30 months and 3 years of treatment (6).

Visual field preservation was also compared in the 1-year clinical trials (4) and in the 3-year study extension (6). After year one, 94% of all subjects had unchanged or improved visual fields (defined as within 5 decibels of baseline) after 12 months. At the end of year 3, 95% of evaluable patients in the brimonidine and timolol groups showed no change or improvement from baseline. No significant differences were seen between treatment groups during years 1 and 3.

Four-year results

Patients from the same seven study sites were re-enrolled after completing the 3-year study (month 36), and were re-evaluated at months 39, 42, 45, and 48 (7). During this further extension stage of the study comparing brimonidine with timolol, the trough IOP-lowering effect that was equivalent for both compounds by the end of year 3 (6), was sustained throughout the fourth year. There were no significant differences in IOP-lowering efficacy between groups at trough ($p \geq 0.231$), with an overall mean reduction from baseline IOP of 4.9 mmHg with brimonidine (range 4.84 to 5.96 mmHg) and 6.08 mmHg with timolol (range 5.69 to 6.44 mmHg). Similarly, throughout year 4, both drug regimens continued to significantly lower mean IOP at peak ($p < 0.001$), with an overall mean reduction from baseline of 8.14 mmHg in the brimonidine group and 6.76 mmHg (p = 0.136) in the timolol group. These year-4 results are consistent with the observations made during year 3, suggesting that the substantial IOP-lowering efficacy of brimonidine, both at peak and at trough, is maintained when used continuously for the long-term management of ocular hypertension and glaucoma.

At the end of year 4, visual fields were relatively unchanged or improved in 93% of patients in the brimonidine group and 91% of the timolol groups (7). Because visual field preservation is the ultimate out-

come measure for therapeutic effectiveness in glaucoma, these results demonstrate that brimonidine is indeed as effective as timolol for the chronic management of glaucoma.

Additional studies comparing brimonidine and beta-blocker monotherapy

Two 4-month multicenter, double-blind trials were performed to compare brimonidine 0.2% b.i.d. with timolol 0.5% b.i.d. (10) and betaxolol 0.25% suspension b.i.d. (11) in patients who were naïve to medical treatment. In these studies, clinical success was assessed by the investigators, using their professional evaluations of IOP-lowering efficacy, safety, patient tolerability and impact on patient quality of life.

In the study comparing brimonidine with timolol, both medications provided comparable initial clinical success rates [71% (75/106) with brimonidine *vs* 70% (73/105) with timolol] (10). The overall mean decreases in IOP were 6.5 mmHg with brimonidine and 6.2 mmHg with timolol. Equal percentages of patients (18%) were switched to the other drug regimen at month 1 due to either lack of efficacy, adverse events, or other reasons as determined by the masked-investigator. Furthermore, similar percentages of patients were considered clinically unsuccessful at month 4 due to inadequate IOP-lowering (6.6% with brimonidine *vs* 9.5% with timolol), or adverse events (4.7% with brimonidine *vs* 2.8% with timolol).

In the second study which compared brimonidine with betaxolol, clinical success with brimonidine as initial therapy was achieved in 74% of glaucoma and ocular hypertension patients, which is consistent with results obtained in the study comparing brimonidine with timolol. This compared favorably with the 57% of patients treated with betaxolol ($p = 0.027$) (11). The overall mean IOP decrease from baseline was 5.9 mmHg for brimonidine and 3.8 mmHg for betaxolol. Both treatments were well tolerated.

In addition, a separate analysis of a subgroup of patients from the 1-year comparative study with timolol focused on patients who were on concomitant systemic beta-blocker medication while participating in the study. This analysis has shown that while the IOP reduction with brimonidine was not influenced by the concurrent systemic beta-blocker treatment, the IOP lowering achieved with timolol was inferior in patients on beta-blocker therapy (8).

The results of these trials in newly diagnosed and naïve patients, which equally consider the IOP-lowering efficacy, safety, patient tolerability, and impact on patient quality of life, suggested that therapy with brimonidine leads to initial clinical success rates comparable with timolol and superior to betaxolol.

Long-term safety

Brimonidine and timolol continued to be well tolerated through 4 years of treatment, with no significant differences between groups in the incidence of any adverse event and with few patients discontinuing the study.

The allergic conjunctivitis associated with prolonged brimonidine treatment was reported to occur at an overall rate of 12.7% of patients over 1 year (4). In the extension study, the ocular allergy rate with brimonidine therapy was reported to drop to 4.2% during year 3 of continuous use (6). The finding of "ocular allergy" with brimonidine has raised several questions and interpretations: it does not include the typical signs and symptoms of a true allergic reaction, there is no cross reactivity with apraclonidine and patients who were allergic to the latter did not react when treated with brimonidine (9). In all cases, the "allergy" was mild-to-moderate in severity and all symptoms and signs resolved rapidly after discontinuation of the drug.

Studies of brimonidine as adjunctive therapy

Recent, postmarketing clinical evaluations have demonstrated that brimonidine is efficacious and well tolerated as adjunctive therapy when added to other classes of agents such as beta-blockers.

In a 3-month study brimonidine 0.2% b.i.d. was compared with pilocarpine 2% t.i.d., when both medications were used adjunctively to a beta-blocker. Brimonidine had a comparable additive ocular hypotensive efficacy to that of pilocarpine, but with fewer adverse ocular side effects (12).

In another study, brimonidine 0.2% b.i.d. was compared with dorzolamide 2% t.i.d., also as additives to timolol 0.5% b.i.d. Brimonidine was significantly more efficacious than dorzolamide ($p = 0.006$) when given in combination with beta-blockers (13). In this study, significantly more patients reached their IOP

reduction goals (≥ 15% reduction from baseline IOP on beta-blocker monotherapy) with brimonidine than dorzolamide after 1 month (86.3% *vs* 67.1%; p = 0.005) and after 3 months (77.8% *vs* 44.4%; p = 0.006).

Other studies compared brimonidine 0.2% b.i.d. with latanoprost 0.005% q.d. as adjunctive therapy and found that brimonidine was similar in efficacy and probably more predictable than latanoprost when used as an adjunctive agent (14, 15). In one of these studies (15), 85% (17/20) of brimonidine and 65% (13/20) of patients treated with latanoprost (p = 0.144) achieved their IOP reduction goals (≥ 15% from baseline) after 1 month while using test medications as adjunctive therapy to beta-blockers (15).

Studies of brimonidine as replacement therapy

In the management of glaucoma, when a certain drug does not obtain an adequate IOP reduction, the option to *replace* rather then *add* a second medication is often adopted. This regimen has the advantage of better compliance, less drug-to-drug interaction, lower costs and fewer side effects.

To examine the efficacy and safety of brimonidine 0.2% b.i.d. as a replacement therapy for patients uncontrolled on their present mono- or adjunctive therapy, a *post-hoc* evaluation of patient records was performed from a large multicenter study based on clinical practice (16). In this 2-month, open-label study involving 460 patients with open-angle glaucoma or ocular hypertension, brimonidine was used as replacement therapy and consistently produced additional mean IOP reductions from pre-brimonidine treatment baseline regardless of the previous monotherapeutic or adjunct therapeutic regimen. Overall, brimonidine replacement therapy significantly reduced mean IOP from pre-brimonidine treatment baseline by an additional 2.3 mmHg (9.8%; p = 0.001). While brimonidine effectively replaced all medications tested, some replacement regimens showed particularly good responses:

- When used as replacement for betaxolol monotherapy an additional mean IOP reduction of 13.56% (p = 0.001) was seen.
- When replacing latanoprost monotherapy, mean IOP was reduced by an additional 12.44% (p = 0.003).
- When replacing latanoprost in an adjunct regimen, mean IOP was reduced by an additional 16.08% (p = 0.010).

In addition to showing broadly effective IOP-lowering capability as replacement therapy in this study, brimonidine was generally well tolerated, appeared safe, and may have had a positive impact on quality of life of patients (16). More than 92% of responding physicians rated brimonidine replacement therapy as excellent or good in comparison to other available medications, with none giving it a rating of poor. Fewer than 7% of patients reported an adverse event, and 4 of 5 quality of life survey scores (Glaucoma Disability Index Survey) (17) showed significant improvement (p < 0.05) from pre-brimonidine treatment baseline during this 2-month study.

In another 2-month study 42 patients with glaucoma or ocular hypertension were examined to evaluate the IOP-lowering efficacy of brimonidine 0.2% b.i.d. (given as replacement for previous two-line therapy) (18). Brimonidine produced an equivalent or greater IOP-lowering effect than the previous two-line regimen in more than 55% of patients tested. Moreover, an equal or additional reduction in mean IOP was seen in more than:

- 50% of patients switched from beta-blocker plus latanoprost.
- 55% of patients switched from beta-blocker plus dorzolamide.
- 80% of patients switched from beta-blocker plus pilocarpine.

The results of this study and those of Lee et al (16) suggest that brimonidine is a reliable alternative for patients who are unsuccessful on their present one- or two-line medication regimen. As mentioned earlier, such substitution may offer cost effectiveness, improved patient compliance and a reduction in the risk of adverse events.

CONCLUSIONS

Brimonidine 0.2% b.i.d., whether given as mono- or adjunctive therapy in clinical trials, invariably appeared safe, even after 4 years of continuous use. Furthermore, after four years of clinical experience, brimonidine continues to appear well tolerated without major effects on patients' quality of life. No clinically significant effects on heart rate, blood pressure, or pulmonary function have been seen with brimonidine, and there have been no published reports of any

serious drug-related adverse events in adults. This highly favorable systemic safety profile makes brimonidine 0.2% b.i.d. an appropriate first-line therapeutic.

Other than ocular allergy in 4.2% to 12.7% of patients (frequency depending on duration of therapy), and symptoms of drowsiness and fatigue leading to discontinuation in 2.7% of patients over the first year of therapy, there appears to be few limiting side effects associated with long-term brimonidine therapy. All of the known brimonidine-associated side effects including ocular allergy and fatigue drowsiness are reversible and easily remedied. Moreover, all known side effects of brimonidine are generally minor and transient, and have little impact on patients' quality of life. However, the use of topical brimonidine should be avoided in newborns or young infants in which CNS depression has been reported (19, 20). This adverse event is most likely a result of differences in drug catabolism and is due to the immaturity of the blood–brain barrier (21, 22).

Clinical studies have shown that brimonidine monotherapy is comparable or superior to beta-blockers. Long-term clinical study data show that this profile is consistent after 4 years. Furthermore, when added to beta-blockers as adjunctive therapy, brimonidine is superior to dorzolamide, similar in efficacy but better tolerated than pilocarpine, and more predictable than latanoprost. Data from replacement studies indicate that brimonidine is a reliable alternative for patients who are unsuccessful on their present one- or two-line medication regimen.

The favorable safety and tolerability profile of brimonidine, combined with its good efficacy, makes it an agent of choice in treating patients with glaucoma, either as monotherapy, adjunctive therapy, or replacement therapy for patients who do not obtain adequate IOP reduction, or suffer from side effects, on their existing regimens. Switching medication in this way may lead to better compliance, less drug-to-drug interaction, lower costs, fewer side effects and, most importantly, better delivery of care to glaucoma patients.

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