

Criteria for Visual Field Progression

Insights from the Collaborative Normal-Tension Glaucoma Study and the Early Manifest Glaucoma Study.

BY DONALD BUDENZ, MD, MPH

Ophthalmologists see patients with established glaucoma every 3 to 6 months to ensure that their IOP is within the targeted range and to assess the stability of the disease. The importance of monitoring progression cannot be overemphasized, because the decisions based on it can be profound. Progressive disease usually necessitates escalating therapy, which may require aggressive treatment such as laser or surgical treatment.

In current, accepted practice, physicians base their assessment of glaucomatous progression on visualizations of the optic nerve and/or visual field testing. The AAO has not endorsed the use of newer imaging technologies for the following of glaucomatous progression, and physicians do not commonly use them. I suspect that most clinicians largely determine disease progression through their interpretation of the gray-tone printout or pattern deviation plot on visual field tests. These subjective methods are less accurate than judgments based on the criteria tested and found to be sensitive and specific within certain probability levels by large clinical trials.

This article describes the criteria from the Collaborative Normal-Tension Glaucoma Study (CNTGS) and the Early Manifest Glaucoma Trial (EMGT) upon which physicians may reliably base their decisions for further treatment.

THE CNTGS

In the CNTGS, investigators developed excellent criteria for the monitoring of glaucomatous visual field progression.^{1,2} Relying solely on visual field analyses to define the endpoint for glaucomatous progression, researchers sought to determine whether lowering IOP in patients with normal-tension glaucoma slowed or prevented progression of the disease. Partway through the study, the investigators checked the progression rate and determined that at least two additional confirmatory fields were necessary to avoid a false-positive determination of progression.

The CNTGS' investigators determined progression using

the threshold numbers in full-threshold Humphrey Visual Fields. If two or more points within or adjacent to an existing scotoma worsened by at least 10 dB or three times the average of the short-term fluctuations, whichever was larger, that field was thought to have progressed after confirmation on two subsequent fields. These numbers, however, may not apply to Swedish Interactive Threshold Algorithm (SITA) visual fields for two reasons. First, the short-term fluctuation is not measured in the SITA program. Second, a 10-dB change in full threshold may not be equivalent to a 10-dB change in a SITA field.

In clinical practice, the importance of this finding is that a large proportion of the results from a single visual field test will yield a false positive. The CNTGS suggested that one confirmatory test is not sufficient. False positives will still exist, even when relying on two fields. Therefore, clinicians should obtain a second, or even a third, confirmatory visual field test before deciding that a patient's disease has progressed and altering their management strategy.

THE EMGT

In the EMGT, patients with early "high-pressure glaucoma" were randomized to receive treatment or not.³ The investigators used visual field testing and flicker chronoscopy, which is a photographic way to examine the optic nerve for progression. Virtually all of the study's patients showed progression in their visual fields before changes occurred in their optic nerves.

As opposed to the relatively arbitrary criteria developed by investigators in the CNTGS and outlined previously, researchers for the EMGT tested subjects four times in 2 months to determine the amount of noise in a visual field test. Once the investigators established the amount of noise, they were able to separate noise from true progression up to a certain statistical probability. The Glaucoma Progression Analysis software (Carl Zeiss Meditec Inc., Dublin, CA) incorporates the EMGT's statistical method for identifying glaucomatous progression. For the indication of *likely pro-*

gression, the Glaucoma Progression Analysis software requires that three consecutive visual field tests contain three or more identical points that have changed at a statistically significant level.

CAVEATS

One should not assume that all visual field progression is due to glaucoma. Patients with glaucoma are generally elderly and either have or can develop other diseases. The practitioner should rule out other causes of a worsening visual field such as vascular occlusive disease, age-related macular degeneration, nonglaucomatous optic neuropathies, and even central nervous system lesions or strokes. Before changing a patient's management, one should obtain at least two, preferably three, confirmatory visual fields—a potentially challenging clinical practice. Without these confirmatory visual fields, physicians may diagnose progression when there is not any. The investigators from the CNTGS and EMGT agree that confirming progression with more than one follow-up field is critical.

THE FUTURE OF DETECTION

Most research shows that changes in the optic nerve and retinal nerve fiber layer are detectable earlier than the changes in visual fields, at least with white-on-white perimetry. By following visual fields only, the clinician may miss early progression. Ideally, practitioners should obtain baseline stereo optic disc photographs and compare new stereophotographs of the optic disc to them on an annual basis. Perhaps a more economically feasible compromise would be to obtain baseline stereophotographs of the optic disc and use them as a basis for comparison during an annual funduscopy examination.

Diagnosing glaucomatous progression can be difficult, especially using visual fields, which tend to vary over time. The Glaucoma Progression Analysis software can help physicians decide whether visual fields have progressed. It should always be used in clinical context, however. □

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ALPHAGAN® P

(brimonidine tartrate ophthalmic solution) 0.15% sterile

INDICATIONS AND USAGE

ALPHAGAN® P is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

ALPHAGAN® P is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS

General: Although **ALPHAGAN® P** ophthalmic solution had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

ALPHAGAN® P has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

ALPHAGAN® P should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients: As with other drugs in this class, **ALPHAGAN® P** ophthalmic solution may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Drug Interactions: Although specific drug interaction studies have not been conducted with **ALPHAGAN® P**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), anti-hypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **ALPHAGAN® P** ophthalmic solution in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after **ALPHAGAN® P** administration are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved 86 and 55 times, respectively, the plasma drug concentration estimated in humans treated with one drop of **ALPHAGAN® P** ophthalmic solution into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of in vitro and in vivo studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility due to **ALPHAGAN® P**.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to **ALPHAGAN® P** ophthalmic solution. Dosing at this level produced an exposure that is 189 times higher than the exposure seen in humans following multiple ophthalmic doses.

There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. **ALPHAGAN® P** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50% - 83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

The safety and effectiveness of brimonidine tartrate ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine tartrate ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years. (Also refer to Adverse Reactions section.)

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

Adverse events occurring in approximately 10-20% of the subjects included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus.

Adverse events occurring in approximately 5-9% of the subjects included: burning sensation, conjunctival folliculosis, hypertension, oral dryness, and visual disturbance.

Events occurring in approximately 1-4% of subjects included: allergic reaction, asthenia, blepharitis, bronchitis, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, flu syndrome, follicular conjunctivitis, foreign body sensation, headache, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, stinging, superficial punctate keratopathy, visual field defect, vitreous floaters, and worsened visual acuity.

The following events were reported in less than 1% of subjects: corneal erosion, insomnia, nasal dryness, somnolence, and taste perversion.

The following events have been identified during post-marketing use of **ALPHAGAN®** ophthalmic solution in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **ALPHAGAN®**, or a combination of these factors, include: bradycardia; hypotension; iritis; miosis; skin reactions (including erythema, eyelid pruritus, rash, and vasodilation) and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving **ALPHAGAN®** ophthalmic solution.

OVERDOSAGE

No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of **ALPHAGAN® P** in the affected eye(s) three times daily, approximately 8 hours apart.

ALPHAGAN® P ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

Rx Only

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U.S. Pat. 5,424,078; 5,736,165; 6,194,415; 6,248,741; 6,465,464; 6,562,873; 6,627,210; 6,641,834; 6,673,337

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