

The GPA Software

Advice for making the most of this diagnostic tool.

BY DONALD BUDENZ, MD, MPH

The Glaucoma Progression Analysis (GPA) software has been available for the Humphrey Field Analyzer (HFA) II (both Carl Zeiss Meditec Inc., Dublin, CA) for just over 1 year. The program is designed to facilitate the diagnosis of glaucomatous progression by means of visual field criteria and a sound statistical method based partly on the Early Manifest Glaucoma Trial (EMGT).¹ The software is analogous to the old Glaucoma Change Probability software of the HFA I (both Carl Zeiss Meditec Inc.). That program analyzed individual points in the visual field for worsening and produced an easily readable printout detailing the probability of an individual point's worsening (Figure 1). Whereas the Glaucoma Change Probability program analyzed total deviation, the GPA software analyzes pattern deviation.

ROOTS IN THE EMGT

Understanding how the GPA software works entails knowing how the EMGT defined progression of the disease. The study was designed to determine whether treating patients with early glaucoma helped to delay or prevent its progression, and reports appearing in the literature during the past 2 years have demonstrated that this is indeed the case.² The two endpoints used in the EMGT were a change in the optic disc's appearance as determined by flicker chronography or a change in visual field, for which the investigators developed their own criteria based on the old GPA software of the HFA I.

As part of the development of the GPA software, a group of patients with glaucoma and a group of normal subjects underwent full-threshold, Swedish Interactive Threshold Algorithm (SITA) Standard, and SITA Fast testing four times over the course of 2 months. In its definition of progression, the GPA software follows the EMGT's criteria by looking for three or more points that show worsening at the 5% level in the exact same location on three or more consecutive visual field examinations. If the criteria are met, the message *likely progression* appears on the GPA printout.

USING THE GPA SOFTWARE

The GPA software averages the first two reliable full-threshold or SITA Standard visual fields for a patient and

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creates a baseline. The program then compares subsequent visual fields to this baseline. If a particular value falls outside the range of noise, that individual point is labeled as *possibly worse* ($P < 5\%$ deterioration) with a designator of an open triangle. Studies have shown that visual fields fluctuate a lot and that practitioners should not base their determination of progression on a single visual field.³

The decision of when to perform subsequent visual field testing depends on how serious the clinician thinks the damage to the visual field is or how rapidly the disease seems to be progressing. A strong suspicion of severe or rapid progression motivates me to conduct repeat testing in the next 1 to 2 weeks and a possible escalation of therapy. For glaucoma suspects or patients with early glaucoma who have no other indications of worsening, waiting longer may be all right. Again, the first visual field to indicate progression generally is not a cause for alarm, because variability in testing is common and the next visual field may revert to the baseline.

On the second confirmatory visual field, the open triangles will be filled halfway with black if the same points show change from the baseline. If three or more half-filled triangles appear on the second follow-up field, the software will label the result *possible progression*. Many patients' results will revert to the baseline after two fields that seem to demonstrate worsening. As shown in the Collaborative Normal Tension Glaucoma Trial, more than two visual fields are necessary to demonstrate worsening.³

Black triangles will appear if the same points exhibit change from the baseline on the third follow-up visual

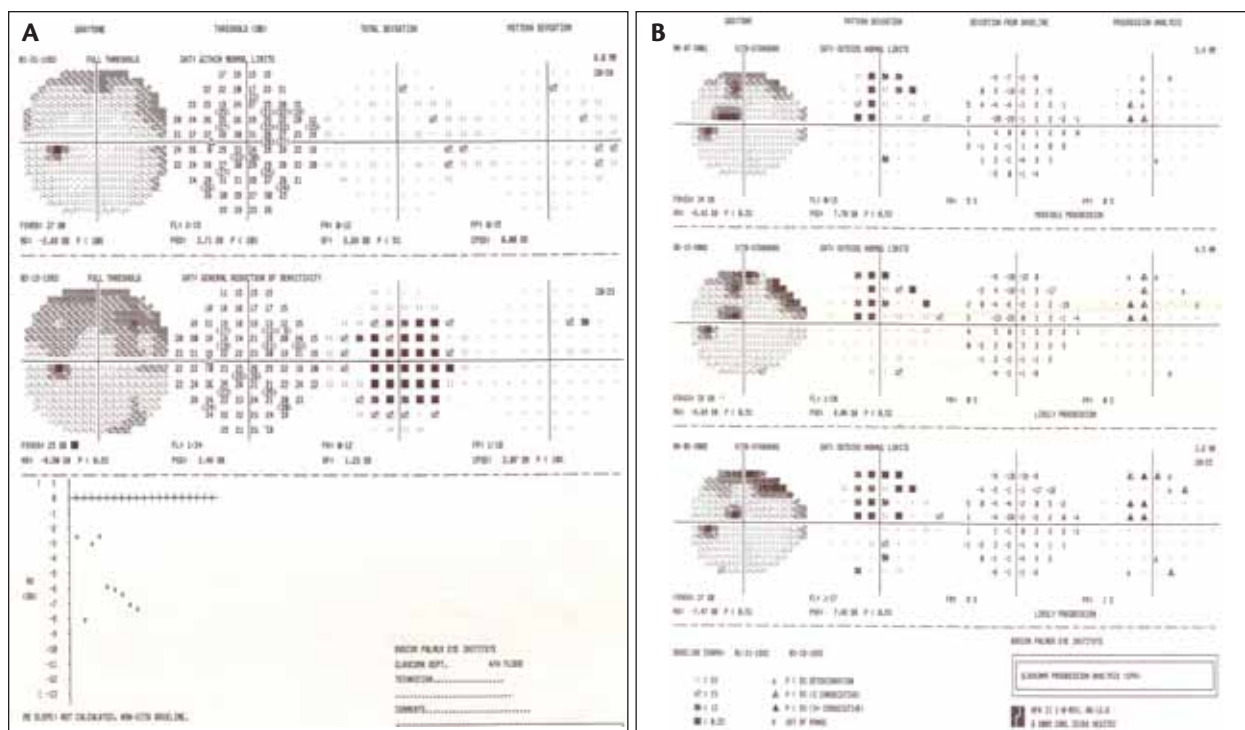


Figure 1. The GPA software has selected two baseline fields (A). Follow-up visual fields indicate possible and, finally, likely progression in a patient with glaucoma (B).

field as did on the first and second follow-up visual fields. If three or more black triangles appear on the third follow-up, the program will label the result *likely progression*, and the patient will have reached the end-point of glaucomatous progression according to the EMGT.

One of the GPA software's strengths is that it can compare follow-up SITA fields to full-threshold baseline visual fields. The program cannot compare a new full-threshold visual field with older SITA tests, however.

DIFFERENTIAL DIAGNOSIS

One caveat is that not all worsening of visual fields is due to glaucoma. A complete ocular examination is necessary to rule out retinal disease (eg, vascular occlusive disease) and other diseases of the optic nerve such as compressive neuropathy or ischemic optic neuropathy. If these alternate causes are absent, however, glaucomatous progression is the probable diagnosis.

The GPA software assists clinicians in determining whether worsening of the visual field is due to glaucoma or another cause. It takes into account age-related changes that lessen sensitivity and changes in the field due to diffuse depression from cataract or other media opacity such as corneal edema or vitreous hemorrhage. The program subtracts these other factors and focuses

on localized changes, which are more characteristic of glaucomatous progression.

PEARLS

Clinicians must be careful in their selection of baseline fields. The GPA software will automatically choose the earliest two reliable visual fields and average them to create a baseline. The program is not as good as the practitioner at recognizing artifacts (eg, from small pupils, edge artifact, or lid artifact). The clinician should therefore review the two baseline visual fields selected by the software to ensure that they are appropriate choices. If they are not, it is easy to select two different baseline fields.

In cases of glaucomatous progression involving the setting of a new target IOP or after glaucoma surgery, it is important to reselect the baseline visual fields. In other words, one should compare future testing with a visual field taken at the time of progression rather than before it occurred. Otherwise, the GPA software will flag every subsequent visual field as positive for progression.

THE FUTURE

The GPA software has not been tested against a comparable gold standard, partly because none exists. Neither does the literature contain a study that clearly

demonstrates whether the program works. My colleagues and I, therefore, are conducting a study to test the software on two groups of patients, one with progressing glaucoma and the other in whom the disease is stable. The study will analyze the specificity of the GPA software. We have performed SITA testing five times over 2 months in 50 patients with glaucoma. We will review the results to determine if the software erroneously flags any subjects as progressing.

"[Our study has] two groups of patients, one with progressing glaucoma and the other in whom the disease is stable. The study will analyze the specificity of the GPA software."

Determining the GPA software's sensitivity is more difficult. We plan to identify a group of patients whose disease has definitely progressed by other standard visual-field criteria and then put these fields through the GPA software to check if the program recognizes the progression.

CONCLUSION

Currently, I do not use the GPA software for every patient but rather reserve it for individuals whose disease I suspect to be progressing. The program helps me to determine the status of their glaucoma with some statistical probability. We are moving toward using the GPA in the routine management of glaucoma patients at the Bascom Palmer Eye Institute in Miami, 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® P** 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® P**, 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® P** ophthalmic solution.

OVERDOSAGE

No information is available on overdose 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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