Results of the European Glaucoma Prevention Study

*The European Glaucoma Prevention Study (EGPS) Group**

Objective: The European Glaucoma Prevention Study (EGPS) seeks to evaluate the efficacy of reduction of intraocular pressure (IOP) by dorzolamide in preventing or delaying primary open-angle glaucoma (POAG) in patients affected by ocular hypertension (OHT).

Design: Randomized, double-masked, controlled clinical trial.

Participants: One thousand eighty-one patients (age, ≥30 years) were enrolled by 18 European centers. The patients fulfilled a series of inclusion criteria, including: IOP 22 to 29 mmHg; 2 normal and reliable visual fields (on the basis of mean deviation and corrected pattern standard deviation or corrected loss variance of standard 30/II Humphrey or Octopus perimetry); normal optic disc as determined by the Optic Disc Reading Center.

Intervention: Patients were randomized to treatment with dorzolamide or placebo (the vehicle of dorzolamide).

Main Outcome Measures: Efficacy end points were visual field, optic disc changes, or both. A visual field change during follow-up had to be confirmed by 2 further positive tests. Optic disc change was defined on the basis of the agreement of 2 of 3 independent observers evaluating optic disc stereo slides. The safety end point was an IOP of more than 35 mmHg on 2 consecutive examinations.

Results: During the course of the study, the mean percent reduction in IOP in the dorzolamide group was 15% after 6 months and 22% after 5 years. Mean IOP declined by 9% after 6 months and by 19% after 5 years in the placebo group. At 60 months, the cumulative probability of converting to an efficacy end point was 13.4% in the dorzolamide group and 14.1% in the placebo group (hazard ratio, 0.86; 95% confidence interval [CI], 0.58–1.26; $P = 0.45$). The cumulative probability of developing an efficacy or a safety end point was 13.7% in the dorzolamide group and 16.4% in the placebo group (hazard ratio, 0.73; 95% CI, 0.51–1.06; $P = 0.1$).

Conclusions: Dorzolamide reduced IOP by 15% to 22% throughout the 5 years of the trial. However, the EGPS failed to detect a statistically significant difference between medical therapy and placebo in reducing the incidence of POAG among a large population of OHT patients at moderate risk for developing POAG, because placebo also significantly and consistently lowered IOP. *Ophthalmology 2005;112:366–375 © 2005 by the American Academy of Ophthalmology.*

Prevention of glaucomatous damage remains one of the major goals in ophthalmology. At present, the therapeutic strategies largely are based on a medical or a surgical approach aimed at decreasing intraocular pressure (IOP). Ocular hypertension in fact has been recognized as the most important risk factor for the development of primary open-angle glaucoma (POAG)[1–5] and, as of today, the only factor that can be controlled medically or surgically. Among other risk factors, such as age, race,[3] family history,[5,6] and low diastolic perfusion pressure,[4,5,7] which are deemed important in the genesis of the disease, only the last one hypothetically can benefit from a multidisciplinary therapeutic approach. Because elevated IOP is associated with the development of glaucoma[1,2,8] and topical therapy is capable of reducing IOP, it is conceivable that topical IOP-lowering therapy may protect against the development of glaucoma. This hypothesis has been supported by the Ocular Hypertension Treatment Study (OHTS), which has shown that a 20% IOP reduction from baseline achieved by topical medical therapy may delay or prevent the onset of POAG over the course of 5 years in individuals with elevated IOP.[9] A number of drugs have been demonstrated to be effective in lowering IOP. Among those, traditional categories include β-blockers, parasympathetic agonists, systemic carbonic anhydrase inhibitors, and sympathetic agonists. Newer categories effective in reducing IOP include prostaglandin analogs, α^2 agonists, and topical carbonic anhydrase inhibitors. Although all of these drugs are capable of reducing IOP, at the time the European Glaucoma Prevention Study (EGPS) was designed clear evidence of their own specific efficacy in reducing the incidence of glaucoma did not exist.[10–12]

On the basis of these observations, we designed the EGPS, an investigator-initiated trial, to test the hypothesis

Originally received: May 18, 2004.
Accepted: November 15, 2004. Manuscript no. 240378.

Supported by The European Commission, Brussels, Belgium (BIOMED II program, contract no.: BMH4-CT-96-1598), and Merck & Co., Inc., Whitehouse Station, New Jersey.

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*See "Appendix" for a list of the group's members, and "Acknowledgments" for writing committee identification.

ISSN 0161-6420/05/$–see front matter
doi:10.1016/j.ophtha.2004.11.030

that the onset of POAG (defined on the basis of visual field loss, optic disc change, or both) can be prevented or delayed in patients with increased IOP by means of medical hypotensive therapy. Secondary aims of the EGPS were to obtain information about the natural history of ocular hypertension (OHT) and the identification of risk factors in the onset of POAG. The protocol was submitted to, approved by, and received funding from the BIOMED II Program of the European Commission. At the time the study was designed and approved (June 1995), commercially available medications for OHT in the 4 European countries participating in the study were limited to topical β-blockers, dorzolamide, and older drugs, including oral carbonic anhydrase inhibitors and parasympathetic and sympathetic agonists.

The hypotensive drug selected for use in the EGPS was dorzolamide. Clinical studies in humans have demonstrated that dorzolamide is well tolerated and possesses good IOP-lowering activity.[13–19] Three times daily administration of 2% dorzolamide results in a substantial mean percent decrease in IOP of 18% to 22%[18] and of 14% to 20%[19] throughout the day. As soon as the study was approved by the European Commission, the manufacturer of dorzolamide (Merck & Co., Inc., Whitehouse Station, NJ) was approached and agreed to participate in the study by providing the study drug and any additional support.

In this article, we describe the efficacy of medical treatment (by topical dorzolamide) as compared with placebo in delaying or preventing the onset of POAG in OHT patients. Analyses on prognostic and predictive factors will be the subject of future articles.

Patients and Methods

The EGPS was a multicenter, randomized, double-masked, placebo-controlled clinical trial. The design and methods of the EGPS were described previously[20] and are summarized as follows.

Study Organization

The EGPS organization consisted of 18 centers distributed in 4 European countries: Belgium, Germany, Italy, and Portugal, listed at the end of this article. The Coordinating Center was responsible for eligibility confirmation, end point confirmation, quality assurance, and data processing. The Data Management and Statistical Analysis Center was responsible for epidemiologic and biostatistical input, data management and analysis, and report preparation. A centralized optic disc archiving center provided the optic disc stereo slides of each participant to the Optic Disc Reading Committee, which was composed of 3 independent, certified evaluators.[21] Visual field assessment at enrollment was performed at each study center by the local investigator. The assessment of visual field end points was performed at the Coordinating Center. The Steering Committee was composed of the principal investigators from each of the 4 participating countries, the biostatistician responsible for the data management and biostatistical center, an American glaucoma specialist, and a representative from Merck.

The study protocol was approved by the ethical review committees of each center. The ethical conduct of the study and the information concerning adverse and beneficial treatment effects were monitored by a Data and Safety Monitoring Committee (DSMC). Only the DSMC was aware of evidence of treatment effects (in terms of knowing the study results in the 2 arms) during the course of the study. For the interim analyses, the DSMC was assisted by an unmasked statistician (a nonvoting member of the DSMC) who was otherwise uninvolved in this study.

Study Protocol

The eligibility criteria included age between 30 and 80 years, a qualifying IOP between 22 and 29 mmHg in at least 1 eye (without therapy or after a washout of at least 3 weeks from previously used drugs), gonioscopically open angles, 2 normal and reliable visual field tests per eye as determined by the local investigator, and normal optic discs seen at clinical examination and on stereoscopic photographs as determined by the 3 independent evaluators of the Optic Disc Reading Center. Exclusion criteria included a visual acuity of worse than 20/40 in either eye, previous intraocular surgery, or any sign of diabetic retinopathy or other diseases capable of causing visual field loss or optic disc deterioration. Informed consent, prepared according to the ethical review committees' regulations, was obtained from each participant. Eligible patients were consecutive cases from clinic populations.

Methods

The patients were randomized into 2 groups: active therapy (dorzolamide) and placebo (which was the vehicle of the active therapy). The placebo was a sterile, isotonic, buffered, slightly viscous, aqueous solution with a pH of approximately 5.6 and an osmolality of 260 to 330 milliosmoles. Ingredients were hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, hydrochloric acid (to adjust pH), and water. Benzalkonium chloride 0.0075% was added as a preservative.

Randomization was obtained at the Coordinating Center. Each clinical center had its own randomization list that was stratified for pseudoexfoliation, pigmentary dispersion syndrome, and diabetes mellitus. Bottles of drug and placebo were given to each center according to the randomization list. Patients were given a bottle marked with a code label. The administration of the drug (or placebo) was the same in both cases and corresponded to the recommended dosage and administration of the active drug (3 times daily). The bottles of active therapy and of placebo were identical in appearance. At each study visit, the patient received enough drug (or placebo) for a 6-month period. Patients were checked at a 6-month interval, at which time they were queried about any missed doses. The allocation code was secured at the Coordinating Center at the office of the Project Coordinator.

Whenever the treatment had to be interrupted, whether because of allergy or other unspecific ocular problems, it was started again after the resolution of the problem itself.

Masking. The EGPS was a double-masked study. Neither the patients nor the investigators visiting or testing the patients knew the group to which they belonged (therapy or control). The evaluation of visual field and optic disc photographs also was performed in a masked fashion.

Study Visit. The baseline and follow-up visits included the assessment of refraction and visual acuity using the procedure routinely used at each given office; Goldmann applanation tonometry performed and recorded by a single investigator between 8:00 and 11:00 AM (i.e., at least 1 but not more than 3 hours after the last dose of study medication); complete ophthalmologic examination, automated static perimetry with a Humphrey or Octopus instrument using a central 30° program with threshold double-crossing strategy; and color slide stereophotography of the optic disc. Gonioscopy was performed at the end of the visit after resolution of mydriasis.

Follow-up visits included an assessment of compliance, checking for possible side effects, and the occurrence of adverse effects.