

150
Floo
12
103
1

AMERICAN
ACADEMY OF
OPHTHALMOLOGY

Volume 103 Number 1
January 1996
ISSN 0161-6420

100
YEARS OF
EXCELLENCE
1896 • 1996

Ophthalmology

*The Journal of the
American Academy of Ophthalmology*

*Eye Care Technology Forum Vision Research
Recommendations*

PRK in Active Duty Military Personnel

Factors Influencing Corneal Graft Survival

Chorioretinopathy in Women

*Latanoprost in Open-angle Glaucoma and
Ocular Hypertension*

Differential Diagnosis of Eyelid Retraction

Ophthalmology
BML 1st & 2nd Floors
UC San Diego
Received on: 02-13-96

Ophthalmology

Journal of the
American Academy of Ophthalmology

The objective of the American Academy of Ophthalmology in publishing its journal, **Ophthalmology**, is to provide opportunities for the free exchange of ideas and information. The Academy accepts no responsibility for any statements published in **Ophthalmology**. These statements are to be attributed solely to their authors and are not, by the fact of their publication in **Ophthalmology** or ownership of copyright, necessarily those of the Academy or **Ophthalmology** or indicative of Academy views or policy or editorial concurrence.

Editor-in-Chief

Don Minckler*

Los Angeles, CA

Associate Editor

Rohit Varma*

Los Angeles, CA

Editorial Board

Douglas R. Anderson
Miami, FL

George B. Bartley
Rochester, MN

Roy W. Beck
Tampa, FL

Mark S. Blumenkranz
Menlo Park, CA

***James D. Brandt**
Sacramento, CA

J. Brooks Crawford
San Francisco, CA

Susan H. Day
San Francisco, CA

Robert C. Drews
Clayton, MO

***Robert Folberg**
Iowa City, IA

William R. Freeman
La Jolla, CA

Brenda L. Gallie
Toronto, Canada

Peter Hamilton
London, England

Glenn J. Jaffe
Durham, NC

***Robert E. Kalina**
Seattle, WA

Yoshiaki Kitazawa
Gifu, Japan

Ronald Klein
Madison, WI

Richard Alan Lewis
Houston, TX

Maureen G. Maguire
Philadelphia, PA

***Joel S. Mindel**
New York, NY

David C. Musch
Ann Arbor, MI

Denis M. O'Day
Nashville, TN

William H. Spencer
San Francisco, CA

Roger F. Steinert
Boston, MA

***Alan Sugar**
Ann Arbor, MI

Andrea C. Tongue
Lake Oswego, OR

Thomas A. Weingeist
Iowa City, IA

Editorial Staff

Ann Dawson

Karyn Crislip

Sherril Nixon

Sue Gertson

Managing Editor

Production Editor

Editorial Assistant

Reference Librarian

* Member, Editorial Advisory Committee

Ophthalmology (ISSN 0161-6420) is published 13 times a year (monthly except September, in which two issues are published) for the American Academy of Ophthalmology, Inc., by Lippincott-Raven Publishers, 12107 Insurance Way, Hagerstown, MD 21740. Business offices are located at 227 East Washington Square, Philadelphia, PA 19106. © Copyright 1996 by the American Academy of Ophthalmology, Inc. Printed in the U.S.A. Second-class postage paid at Hagerstown, Maryland, and at additional mailing offices.

Address for subscription information, orders, or change of address: (except Japan) 12107 Insurance Way, Hagerstown, MD 21740, or call 1-800-638-3030; in Maryland, call collect 301-714-2300. In Japan, contact Igaku-Shoin, Ltd, 1-28-36 Hongo, Bunkyo-ku, Tokyo 113, Japan (phone: 81-3-3817-5675; fax: 91-3-3815-6776). Members' changes of address, American Academy of Ophthalmology, 655 Beach St., P.O. Box 7424, San Francisco, CA 94120.

Annual subscription rates: U.S.: \$135.00 individual, \$205.00 institution, special resident rate \$42.00; Canada and Mexico: \$175.00 individual, \$245.00 institution, \$54.00 special resident rate. The Canadian GST tax of 7% will be added to the subscription price of all orders shipped to Canada. Lippincott-Raven Publishers' GST identification number is 130876246. All other countries (except Japan): \$202.00 individual, \$272.00 institution, \$81.00 special resident rate (prices include \$27.00 air freight delivery; air freight delivery occurs within 7-21 days worldwide). International subscriptions must be prepaid. Single copies \$27.00. (Rates are subject to change.) In Japan, contact Igaku-Shoin, Ltd, 1-28-36 Hongo, Bunkyo-ku, Tokyo 113, Japan. Copies will be replaced without charge if the publisher receives a request within 90 days of the mailing date, both in the U.S. and worldwide.

Advertising inquiries should be addressed to Pharmaceutical Media, Inc., 30 East 33rd St, 4th Floor, New York, NY 10016.

Manuscripts, Letters to the Editor, and requests for permission to use published material should be submitted to the editorial offices of the journal: *Ophthalmology*, Doheny Eye Institute, 1450 San Pablo St, Rm 4900, Los Angeles, CA 90033-4666.

POSTMASTER: Send address changes to *Ophthalmology*, P.O. Box 1550, Hagerstown, MD 21741.

ution

IS
armaceuticals

**DOCKET
ALARM**

Find authenticated court documents without watermarks at docketalarm.com.

Comparison of Latanoprost and Timolol in Patients with Ocular Hypertension and Glaucoma

A Six-month, Masked, Multicenter Trial in the United States

Carl B. Camras, MD, the United States Latanoprost Study Group*

Purpose: Latanoprost, a new prostaglandin analogue, was compared with timolol for ocular hypotensive efficacy and side effects.

Methods: In a multicenter, randomized, double-masked, parallel group study, 268 patients with ocular hypertension or early primary open-angle glaucoma received either 0.005% latanoprost once daily or 0.5% timolol twice daily for 6 months. All except ten patients from each group successfully completed the study.

Results: Intraocular pressure (IOP) was significantly ($P < 0.001$) reduced and maintained by both medications without evidence of a long-term drift over 6 months. Comparing 6-month with baseline diurnal IOP values, the IOP reduction (mean \pm standard deviation) achieved with latanoprost (-6.7 ± 3.4 mmHg) was significantly ($P < 0.001$) greater than that produced with timolol (-4.9 ± 2.9 mmHg). Four patients treated with timolol and none treated with latanoprost were withdrawn from the study because of inadequate IOP control. Pulse rate was significantly reduced with timolol, but not with latanoprost. Slightly more conjunctival hyperemia appeared in latanoprost-treated compared with timolol-treated eyes. Fewer subjective side effects occurred in latanoprost-treated eyes. Both eyes of a patient with a characteristic, concentric iris heterochromia (darker centrally) at baseline showed a definite, photographically documented increase in pigmentation during latanoprost treatment, making the irides uniformly darker. Three additional patients treated with latanoprost were suspects for this color change. Otherwise, no significant difference between treatment groups occurred in visual acuity, slit-lamp examination, blood pressure, and laboratory values.

Conclusion: Latanoprost has the potential for becoming a new first-line treatment for glaucoma *Ophthalmology* 1996;103:138-147

Originally received: October 27, 1994.
Revision accepted: August 31, 1995.

From the Department of Ophthalmology, University of Nebraska Medical Center, Omaha.

* Members of the United States Latanoprost Study Group are listed in the Appendix at the end of this article.

Presented in part at the Glaucoma Society of the International Congress of Ophthalmology in Quebec City, Canada, June 1994, and as a poster at the American Academy of Ophthalmology Annual Meeting, San Francisco, November 1994.

Also submitted for publication, in part, in *Glaucoma Update V*, Krieglstein GK, ed, Springer-Verlag Berlin Heidelberg, which has limited distribution.

Several prostaglandin (PG) prodrugs and analogues are potent, effective, and well-tolerated ocular hypotensive agents in patients with ocular hypertension or glaucoma.^{1,2} Of these agents evaluated in clinical trials,³⁻²³ the 17-

Supported by a grant from Pharmacia Pharmaceuticals, Uppsala, Sweden.

Dr. Camras is a consultant to Pharmacia Ophthalmics, Uppsala, Sweden, and to Alcon Laboratories, Fort Worth, Texas. None of the authors has a proprietary interest in the development or marketing of any drug used in this study or in any competing drug.

Reprint requests to Carl B. Camras, MD, Department of Ophthalmology, University of Nebraska Medical Center, 600 South 42nd St, Omaha, NE 68198-5540.

pheny
the gr
and si
analo
less th
at the
ful in
tant to
numb
perio
onists
poten
 β -blo
ical th
Th
ficacy
13,14
-1-iso
timol
ocula

Pati

Patie

Patier
States
patier
pressu
single
exami
for th
remai
ment
eye; (C
hyper
persio
IOP v
drug t
field p
If t
their r
before
onists
chilir

Pat
any o
age; c
feedin
glauco
specifi
would
narrow
intrao
out fe
norm:
nation
tact le
other

phenyl-substituted PGF_{2α} analogues apparently provide the greatest separation between ocular hypotensive efficacy and side effects.^{8,11,12,15-21,24-26} Previous studies with these analogues have followed only small groups of patients for less than 3 months (Alm et al, unpublished data; presented at the 1993 ARVO Annual Meeting). However, to be useful in treating chronic open-angle glaucoma, it is important to evaluate a drug for efficacy and side effects in large numbers of patients undergoing treatment for extended periods of time. Because nonselective β-adrenergic antagonists are currently the first-line treatment for glaucoma, potentially new therapeutic agents may be compared with β-blockers to establish their relative usefulness in the clinical therapy of glaucoma.

This multicenter, randomized study compares the efficacy and side effects of 0.005% latanoprost (PhXA41; 13,14 - dihydro - 17 - phenyl - 18,19,20 - trinor - PGF_{2α} -1-isopropyl ester) applied topically once daily with 0.5% timolol given twice daily for 6 months to patients with ocular hypertension or glaucoma.

Patients and Methods

Patients

Patients were recruited from 17 centers in the United States. To be eligible for the study, at least one eye of each patient had to meet the following criteria: (1) intraocular pressure (IOP) of at least 22 mmHg with no more than a single ocular hypotensive medication during the screening examination; (2) if only one eye of a patient was eligible for the study, the expectation that the other eye would remain controlled either without treatment or with treatment with the same experimental agent used in the eligible eye; (3) diagnosis of primary open-angle glaucoma, ocular hypertension, exfoliation syndrome, or pigmentary dispersion syndrome; (4) expectation by the investigator that IOP would remain adequately controlled with a single drug treatment for 6 months without optic nerve or visual field progression.

If treated for their elevated IOP, patients discontinued their medication for a minimum of the following intervals before the baseline day: 3 weeks for β-adrenergic antagonists, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists or carbonic anhydrase inhibitors.

Patients were ineligible for inclusion into the study for any of the following reasons: younger than 40 years of age; currently pregnant, considering pregnancy, or breast feeding; use of any ocular medications other than for glaucoma; diagnosis of any glaucoma type other than specified in the inclusion criteria; advanced glaucoma that would be at risk for progression during the washout period; narrow angles or presence of peripheral anterior synechiae; intraocular surgery or argon laser trabeculoplasty carried out fewer than 6 months before the study; corneal abnormalities or other problems preventing reliable applanation tonometry; inability to temporarily suspend contact lens use for the duration of the study; active eye disease other than ocular hypertension or primary open-angle

glaucoma; ocular inflammation less than 3 months before the study; known allergy or contraindication to any medications used in the study (specifically, contraindications to β-blockers, including congestive heart failure, sinus bradycardia, second- or third-degree atrioventricular block, chronic obstructive pulmonary disease, bronchial asthma, etc.); if treated orally with medications known to affect IOP, the expectation that the type or dosage of these drugs would not change during the course of the study; any unstable medical condition; history of noncompliance or unreliability; or inability to adhere to the protocol design.

Protocol

After obtaining appropriate informed consent and approval by the Institutional Review Board at each center, a medical history was taken from each subject, including a list of all systemic medications each was receiving. A complete ophthalmologic history and examination was performed on each patient within 4 weeks of the onset of the study (Table 1).

The protocol used during the 6-month study is described in Table 1. On the baseline day, all of the parameters indicated in Table 1 were assessed. Patients were assigned to treatment by computer-generated randomization, stratified for each center and performed in blocks within each center. Neither the examiners nor the subjects were informed of the identity of the drop received during the course of the study.

Beginning in the evening of the baseline day, one drop (approximately 35 μl) of either 0.005% latanoprost or 0.5% timolol was applied topically to one or both eyes (all eligible eyes) of each of 268 patients. Each patient received two bottles, one carefully labeled for use each morning at 8:00 AM, and the other for the evening at 8:00 PM. The timolol-assigned group of patients received timolol for both doses each day. The latanoprost-assigned group of patients received active latanoprost at 8:00 PM and the vehicle (0.02% benzalkonium chloride, 0.5% monosodium phosphate monohydrate, 0.6% disodium hydrogen phosphate dihydrate, and 0.4% sodium chloride) at 8:00 AM each day. Treatment was continued for 6 months. At 0.5, 1.5, 3, 4.5, and 6 months, the parameters specified in Table 1 were recorded. Patients were told not to take their study medications on the morning of their return visits. After their 8:00 AM examination, their study drops were administered by the study coordinator or by the patient. The treatment code was not broken by the manufacturer until the last patient completed the study and until all case report forms were completed and reviewed for accuracy.

Adverse events were monitored carefully throughout the study. An adverse event was defined as any undesirable event occurring in a subject, regardless if it were considered related to the investigational drug. A serious adverse event was defined as potentially fatal, life threatening, sight threatening, permanently disabling, requiring hospitalization, cancer, or a drug overdose.

are
sive
a.^{1,2}
17-
—
den.
den,
has
used
ogy,
NE

Table 1. Timing of Evaluation

Evaluation	Within 4 Wks of Baseline	Baseline			2 Wks	1.5 Mos	3 Mos	4.5 Mos	6 Mos		
		8 AM	12 Noon	4 PM	8 AM	8 AM	8 AM	8 AM	8 AM	12 Noon	4 PM
Visual fields*	X									X	
Subjective side effects†	X	X		X	X	X	X	X	X		X
Conjunctival hyperemia‡	X	X	X	X	X	X	X	X	X	X	X
Slit-lamp biomicroscopy§	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure	X	X	X	X	X	X	X	X	X	X	X
Blood pressure and pulse rate (resting)	X	X			X		X		X		
Color photography of iris	X						X	X	X		
Blood¶ and urine analysis**	X								X		

* Two visual fields (Humphrey 24-2 or 30-2, or Octopus G-1) required within 6 months before baseline day, at least one of which was done within 4 weeks of baseline.

† Blurred vision, photophobia, itching, burning, stinging, tearing, dryness, foreign body sensation, eye pain, and eyelid pain or discomfort.

‡ Based on a relative scale of 0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 by comparing with standard photographs showing no (0), mild (1), moderate (2), and severe (3) hyperemia.

§ Undilated and dilated slit-lamp biomicroscopic examination of the cornea, anterior chamber, iris, and lens.

|| Goldmann applanation tonometer taking three replicate measurements for each eye using the same calibrated tonometer at each visit.

¶ Complete blood count, differential, platelet count, cholesterol (total, HDL, and LDL), triglycerides, total protein, glucose, creatinine, urea nitrogen, bilirubin, alkaline phosphatase, SGOT, SGPT, sodium, potassium, calcium, and chloride.

** Including evaluation for albumin and sugar.

Demographics and Withdrawals

Of the 268 patients initially enrolled, 128 were assigned to the latanoprost group and 140 to the timolol group. No significant difference in age, sex, race, family history of glaucoma, number of eyes treated per patient, iris color, diagnosis or previous medical therapy existed between the two groups of patients (Tables 2 and 3). Ten patients from each group dropped out of the study for the reasons indicated in Table 4. Four patients receiving timolol and none receiving latanoprost were withdrawn from the study because of inadequate IOP control (Table 4).

Data Analysis

A two-tailed, paired or unpaired Student's *t* test was used as appropriate for statistical evaluation of differences between treatment and baseline values or between the latanoprost and timolol groups. Differences in diurnal IOP values between the latanoprost and timolol groups were determined using analysis of covariance with treatment groups and centers as factors and baseline IOPs as covariants. If both eyes of a patient were treated, a mean value of the two eyes was

used for analysis. Protocol violations prevented inclusion of at least one IOP measurement from each of 24 patients treated with latanoprost and 26 treated with timolol. Overall, 11 patients had one measurement excluded, 28 had 2 excluded, 5 had 3 excluded, 1 had all except baseline measurements excluded (instilled study medication before the 8:00 AM IOP measurement on each visit), and 5 had all excluded (because of insufficient washout of previous β -blocker therapy). Thirty of these patients had the 12:00 noon and 4:00 PM measurements on their 6-month visit excluded because of failure to receive the 8:00 AM dose of the study medication on that day. When analyzed by including, rather than excluding, the IOPs during protocol violations, the significance of the findings did not change.

Results

Intraocular Pressure

Compared with baseline measurements, both latanoprost and timolol caused a significant ($P < 0.001$) reduction of IOP throughout the duration of therapy (Figs 1 and 2).

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.