Contemporary Issue

Gold Standard Medical Therapy for Glaucoma: Defining the Criteria Identifying Measures for an Evidence-Based Analysis

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ABSTRACT

Background: Over the past decade, several new medical therapies have become available for the treatment of primary open-angle glaucoma (POAG). A systematic evidence-based approach for identifying an optimal therapeutic agent is lacking.

Objectives: The aims of this review were to critically evaluate published treatment recommendations for POAG and, based on a systematic review of the literature, to develop criteria that would define a "gold standard" medical therapy that reflects new treatment advances and established therapeutic goals.

Methods: A MEDLINE search spanning the years 1966 to 2002 and using the search terms *gold standard, drug of choice, agent of choice, benchmark, ophthalmology, eye,* and *glaucoma* was conducted and the results reviewed by a panel of 15 experts in the field of glaucoma. Published treatment recommendations for POAG were discussed. Criteria, anchored to medical evidence, for distinguishing a standard of medical therapy for POAG were defined.

Results: The terms connoting a gold standard therapy were found in only 258 of ~368,000 ophthalmology-related citations and 53 of almost 23,000 glaucoma citations, validating the need to define therapeutic standards. The lack of recommendations for the use of new classes of ocular hypotensive agents was acknowledged. Criteria

This article was conceived by consensus at a roundtable discussion held in Vence, France, February 14–15, 2002. Updated information was incorporated as available.

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identified to evaluate intraocular pressure (IOP)–lowering agents as gold standards included the following: efficacy in reducing IOP consistently over a 24-hour period to a level that will preserve the visual field and protect the optic nerve without inducing tachyphylaxis and tolerance, paucity of local and systemic adverse effects, promotion of patient compliance, and applicability in diverse patient populations.

Conclusions: These criteria should be employed as measures for evidence-based analyses to evaluate available and future IOP-lowering medical therapies for POAG. The conceptual framework presented may be applicable to other therapeutic areas. (*Clin Ther.* 2004;26:2102–2120)

Key words: beta-adrenergic blockers, evidence-based medicine, open-angle glaucoma, gold standard, intraocular pressure, prostaglandin.

INTRODUCTION

The Challenge of Managing a Chronic Disease

As improvements in medicine and technology promote longevity, chronic, disabling diseases account for an ever-increasing proportion of death and morbidity. Hypertension, diabetes mellitus, gastroesophageal reflux disease (GERD), asthma, chronic obstructive pulmonary disease, depression, arthritis, and other chronic diseases and impairments afflict more than half of all Americans.[1] These individuals account for a greater proportion of US health care costs than persons without chronic conditions.[2] The World Health Organization (WHO) estimates that by 2020 chronic conditions will contribute two thirds of the global burden of disease.[3] Unfortunately, the effectiveness of health care policy and delivery systems for the management of chronic illness has lagged behind the scientific advances that have supported increases in longevity.[4–6] Moving biomedical research discoveries from bench to bedside requires time. Even when new medical and surgical therapies are approved for use, practitioners and policy makers may still fail to identify and deploy standards of excellence, omissions that often result in variable practice patterns.[7,8]

Chronic diseases pose specific disease-management challenges. Comorbidities, multifactorial causes, and the variety of drug options, the relative value of which is undetermined, often test clinical decision making. Critical analysis of chronic disease study data may be difficult, especially when these studies do not include the extended follow-up needed to adequately draw treatment conclusions. The persistence of chronic diseases requires that physicians also address subjective issues related to the disruption of a patient's normal physical and social function. Discomfort and lifestyle changes can disturb patients and affect their compliance with treatment regimens.[9] To improve patients' experience with chronic disease processes and to predict treatment compliance, treatment decisions should consider quality of life (QOL).[10,11]

Glaucoma as a Chronic Disease

Primary open-angle glaucoma (POAG) represents the major chronic disease concern for ophthalmologists. Its prevalence in the US population ≥40 years of age is estimated to be 1.86%, affecting >2 million individuals.[12] The WHO estimates that global rates of glaucoma and glaucoma-related disability are considerably higher, >6.4 million.[13–15] Glaucoma differs from most other chronic diseases in 2 important respects. Unlike debilitating chronic diseases (ie, arthritis, asthma, GERD, depression), glaucoma is treated in the absence of symptoms. In the severity scale defined by the American Academy of Ophthalmology, "mild" (ie, early) glaucoma includes optic nerve changes without a visual field defect.[10] It is only later in the disease process that patients may become aware of a defect in their vision as a consequence of damage caused by POAG. In a population-based prevalence survey,[16] roughly half of all patients with optic nerve damage from POAG were reported to be unaware that they had the condition. Binocularity can be a factor: compensation decreases the likelihood that patients with monocular deficits will notice gradual visual deterioration.[17] However, evidence suggests that monocular and binocular measures of visual function correlate with patients' assessments of vision.[18] Because measurable retinal nerve fiber damage precedes a patient's perception of visual field loss,[19–21] the motivation to comply with prescribed treatments is often based on the patient's fear of blindness.[22] Transmitting this concern for vision preservation requires that the physician provide the patient with sufficient information to permit an understanding of the complex pathophysiology.

Glaucoma is further distinguished from other chronic diseases by the limited ability of ophthalmologists to directly monitor and assess the disease. Traditional methods of evaluating glaucomatous neuropathy have not provided adequate quantitative data.[23,24] The next generation of quantitative technologies (eg, scanning laser ophthalmoscopic topography of the optic disc, scanning laser polarimetry and optical coherence tomography of the retinal nerve fiber layer) are not yet sufficiently sensitive or specific to independently diagnose or monitor disease progression.[10,24–26] Visual field disturbance is a major functional measure for POAG treatment, but sensitivity limitations of automated static threshold perimetry have precluded reliable measurement of minor changes.[27] Specificity and sensitivity in detecting early glaucomatous visual field changes using standard automated and short-wavelength automated perimetry (SWAP) have been demonstrated.[28–31] However, the sensitivity of SWAP is limited in patients with cataract.[32] New psychophysical tests that may detect early onset or progression of visual function damage are being evaluated and offer promise.[33,34] Until the utility of these new methodologies is well documented, ophthalmologists must rely on intermediate, or surrogate, markers of disease development or therapeutic efficacy.

Elevated intraocular pressure (IOP) is a major causal risk factor for POAG. Because a clear association exists between increased IOP and optic nerve head damage,[35–37] IOP is a valuable surrogate measure of visual function outcome.[38,39] Results of the Ocular Hypertension Treatment Study[40] showed that IOP reduction is effective in delaying or preventing glaucomatous optic disc and/or visual field loss in individuals with ocular hypertension. When baseline pressures of 24 to 32 mm Hg were reduced with topical medication by a mean of 18.4% (4.6 mm Hg), the cumulative probability of developing POAG at 5 years was 4.4% compared with 9.5% in untreated patients ($P < 0.001$). In univariate and multivariate analyses, development of POAG was positively associated with age, vertical or horizontal cup-disc ratio, IOP, and pattern standard deviation. POAG development was negatively associated with central corneal thickness. These patient subgroups had a 24% to 36% risk for damage.[41] Therapies that lower IOP also impede progression of glaucomatous damage in patients with POAG.[39,42–44] Although the use of IOP and other surrogate outcome measures in medicine has been questioned,[45,46] particularly when threshold values that predict pathologic changes and indicate treatment success are undefined, the rationale for lowering IOP and for continued monitoring of IOP reduction in the treatment of POAG is convincing.

MEDICAL MANAGEMENT OF GLAUCOMA

For most of the 20th century, glaucoma was viewed as a multifactorial optic neuropathy due primarily to increased IOP. Accordingly, the primary treatment goal has been to maintain visual function and optic nerve integrity by achieving around-the-clock IOP reduction. The past 3 decades have seen several advances in the medical treatment of glaucoma. The first of these advances occurred in the late 1970s with the introduction of timolol and the shift from the cholinergic agents (eg, pilocarpine, carbachol) and adrenergic agonists (eg, epinephrine, dipivefrin) to the beta-adrenergic blockers as first-line therapy. By the early 1990s, timolol had become the benchmark comparator for Phase III clinical testing of investigational antiglaucomatous drugs. However, conspicuously absent was research showing that IOP reduction by beta-blockers was adequate to arrest progression in manifest disease or to halt the conversion of a high-risk situation into manifest disease.

The mid-1990s ushered in a second phase of development of topical medications to treat glaucoma with the introduction of prostaglandin derivatives, new alpha-adrenergic agonists, and topical carbonic anhydrase inhibitors. This era of technologic growth compelled us to evaluate our practice decisions in a more focused manner. In addition, the availability of rich and varied information has necessitated a systematic assessment of the evidence that guides therapeutic choices. The critical approach that has been most widely accepted in raising standards of patient care is evidence-based medicine.[47]

CURRENT STATE OF EVIDENCE-BASED MEDICINE IN OPHTHALMOLOGY/GLAUCOMA

Patient care has traditionally relied on a combination of informed but unsystematic observation, physiologic rationale, good instinct, and the consensus of clinical experts. Over the years, advances in basic science and the development of powerful clinical research meth-

ods have generated a wealth of information directly relevant to clinical practice. Still, numerous factors can lead clinicians astray as they try to distinguish high- from low-quality evidence in primary studies, systematic reviews, practice guidelines, and other integrative research and as they endeavor to apply these outcomes to identify the most appropriate therapy for an individual patient.[48] Chronic diseases, in particular, are far too complex to expect a simple relationship between a specific therapy and the desired health outcome. A rigorous analysis of evidence can guide us in determining the actual consequences of a practice and its most appropriate use.

Evidence-based medicine is a stepwise process of clinical decision making that includes assessing the clinical problem; identifying gaps in knowledge; framing questions that address the gaps; critically appraising all relevant research evidence; and using the most valid evidence to form a treatment strategy that considers benefits, risks, costs, and a patient's values.[48] A hierarchy of evidence for evaluating different sources of data is shown in **Table I**.[48,49] Interventional case reports, prospective and retrospective observational studies, and uncontrolled clinical series may all provide useful information but are subject to biases that limit their ability to answer many questions.[49] The randomized, controlled clinical trial has been termed the "gold standard" for ensuring scientific validity in the evaluation of therapy.[50] Ideally, treatments should be tested in patients for whom the remedy is sought (N of 1 trial).[48]

Designing and implementing randomized prospective trials to evaluate visual field outcomes are difficult. Nonetheless, this is the measure that most closely reflects functional vision loss. Instead, control of IOP elevation is the standard measure of ocular hypotensive efficacy.[10] The efficacy of POAG treatments cannot be gauged by improvement in symptoms like that of other disorders.

Ophthalmologists have been slow to incorporate evidence-based medicine into practice. A study examining 102 randomized clinical trials published between 1975 and 1991 showed that only 16 trials were adequately designed to determine the effectiveness of medical treatments for POAG and that only 3 used visual field end points.[51] However, the convincing evidence provided by more recently conducted large, prospective trials[39,42] has confirmed that IOP measurement is an invaluable element in the early detection of glaucoma and that its reduction is the current clinical standard for effective management of the disease.

Table I. A strength-of-evidence hierarchy for treatment decisions.[48,49]

Evidence
N of 1 randomized controlled trial
Systematic review of randomized controlled trials (eg, meta-analysis)
Single randomized controlled trial
Nonrandomized controlled trial
Systematic review of observational studies
Single observational study
Cohort
Cross-sectional
Case control
Clinical series
Case review
Case report
Anecdote
Testimony
Theory
Common sense

NEED FOR ESTABLISHING A GOLD STANDARD

Clinical decision making with respect to initial drug therapy is influenced by a variety of factors. Personal experience has an important impact on the manner in which physicians care for patients. Another key factor is the availability of professional literature. Because of the volume of relevant articles in a given discipline and the limited amount of time available to clinicians, reference to the literature may receive low priority.[52] Keeping current by reading journals is challenging for dedicated clinicians.[52] Other challenges are the time and skill needed to assess the validity and relative value of published data. Eddy[53] bluntly characterized the dilemma: "The complexity of modern medicine exceeds the inherent limitations of the unaided human mind." Third-party influence is another prominent element in the process of ophthalmologists' decision making. Sources of this influence include peers, industry, regulatory agencies, and

professional groups providing expert consensus. The latter may be particularly valuable. As in other specialties, standards and guidelines serve to improve practice patterns, induce more effective disease management, and minimize the direct and indirect costs of treatment. Recommendations concerning specific drugs, tests, and procedures provide valuable assistance to practitioners, facilitating improvement in standards of care.[49,53]

To provide guidance for use of the recently introduced therapeutic classes of ocular hypotensive agents, a group of 15 distinguished glaucoma specialists representing worldwide practice and opinion convened at a roundtable discussion in Vence, France, in February 2002. The goals were to first critically evaluate and discuss the published treatment recommendations for POAG[10,54] and then, using an evidence-based approach, create a set of criteria that would aid in the clinical decision-making process, that is, in choosing initial drug therapy for the treatment of glaucoma (the gold standard therapy) and the development of a hierarchy of other pharmacologic agents. This set of criteria would be useful in evaluating drug therapy in any clinical setting. Support for the meeting was granted on request by the panel chairman to Medical Intervention Systems, Parsippany, New Jersey, a medical education firm with experience in developing and organizing programs for ophthalmologists.

CHARACTERISTICS OF A GOLD STANDARD THERAPY

Prior to the roundtable meeting, MEDLINE searches were conducted to determine whether other medical specialists faced with similar rapid pharmacologic advancements had developed criteria to identify hierarchies of drug therapy with the preferred, recommended, common, or established therapy being the gold standard. The search terms *gold standard, drug of (first) choice, agent of (first) choice, standard of care,* and *benchmark* were used. Only abstracts from English-language articles were reviewed. Although a gold standard therapy can evolve into a benchmark for reference comparisons, the current interest was to learn how the concept of gold standard status has been used to signify superiority within a therapeutic category and to determine how this status has been established. The results of the searches are shown in **Table II**. Approximately 6000 citations that used the term *gold standard* were published from 1966 to 2002. In total, *drug of choice* and *agent of choice* were used with similar frequency. The word *benchmark* was found less often. When combined with a search of 4 medical specialties and the findings normalized to account for the total number of publications per specialty, these terms were found to be cited 3-fold more frequently in cardiology and gastroenterology publications and 1.5-fold more frequently in neurology publications than in ophthalmology publications. Narrowing the

Table II. The concept of *gold standard* in the medical literature: Results of a MEDLINE search.*

	Search Terms				
Total Citations in MEDLINE	Therapeutic Group	Gold Standard	Drug(s) of (First) Choice	Agent(s) of (First) Choice	Benchmark
11,000,000	All MEDLINE	5952	5210	576	1212
367,181	Ophthalmology related	160	82	16	0
22,858	Glaucoma	28	24	1	0
553,100	Gastroenterology related	647	466	51	31
1,046,301	Cardiology related	1207	1083	136	86
1,064,111	Neurology related	702	770	50	70
7,946,549	Other	3208	2785	322	1025

*The MEDLINE search determined the presence of terms related to the concept of *gold standard* in abstracts, titles, and key words of all publications from 1966 to January 2002. Subsearching examined uses specifically related to ophthalmology (including *eye* and *optic*), glaucoma, gastroenterology, cardiology, and neurology. (These medical specialties have been leaders in the use of evidence-based medicine in clinical practice. Gastroenterology and cardiology, like ophthalmology, have both medical and surgical treatment options for major diseases.) The number of total citations found in all MEDLINE searches was rounded to the nearest million.

search for ophthalmology by specifying glaucoma yielded only 28 citations.

Although the term *gold standard* was not uncommon in the general medical literature, it was most frequently applied to diagnostics and screening tools (**Table III**). In these cases, the term was used to reflect reliability and validity in diagnosis of specific conditions. *Gold standard* described either a test in which the "standard" was a true calibration reference point (to determine the reliability of results from other tests) or a test considered the best or recommended method. Similarly, a search for the term *gold standard* within abstracts and titles of current National Institutes of Health grants, using the Computer Retrieval of Information on Scientific Projects (CRISP) database, revealed 107 citations (0.18% of all grants) that were restricted to discussions of diagnostics, procedures, and methods.

A subsequent MEDLINE search combined the original search terms with *drug therapy* and found 252 citations that applied to a medical treatment. In a review of these citations, the term *gold standard* often was used to claim superiority. Abstracts of the identified citations were reviewed to determine whether the paper discussed relevant information about the criteria and/or specifications of evidence-based medicine and other diseases used to confirm a gold standard designation. The corresponding papers were obtained and scrutinized for additional details.

The results of these MEDLINE searches were circulated to each panel member before the discussion, and designated members were selected to present the relevant materials to the panel during their meeting. From the discussion, the panel reached a consensus that the most common characteristics or criteria that should be used to define a gold standard were efficacy, long-term safety, tolerability, compliance, simple and reliable dosing, and use as a clinical benchmark. After the meeting, a proceedings document was prepared and circulated to each panel member for review and comment. Panel members' comments were consolidated and integrated into a final document that was approved by all.

The evidence-based review found that with unsurpassed efficacy, safety, and widespread experience and trust by the medical community, specific pharmacologic agents have become accepted as gold standards of therapy (**Table IV**).[55–70] During the discussion, the panel was presented with information from a historical perspective on the development of gold standard therapies for 2 chronic diseases—GERD and POAG—as follows.

Table III. Frequency (no. [%]) of use of the term *gold standard* in publications identified in a MEDLINE search of the literature from 1966 to 2002.

	Literature Topic		
Subtopic	Ophthalmology (75 mentions)*	Glaucoma (28 mentions)	Gastroenterology (556 mentions)†
Diagnosis	36 (48)	13 (46)	364 (65)
Screening	24 (32)	7 (25)	12 (2)
Surgery	5 (7)	3 (11)	60 (11)
Medical treatment	4 (5)	0 (0)	42 (8)
Other	6 (8)	5 (18)	78 (14)

*Some mentions (85/160) were omitted from analysis because they were not ophthalmology related.
†Some mentions (91/647) were omitted from analysis because they were not gastroenterology related.

Omeprazole for Gastroesophageal Reflux Disease

GERD is characterized by symptoms (eg, heartburn and/or regurgitation) and tissue injury resulting from the reflux of gastric material into the esophagus or oropharynx.[71] Like glaucoma, it is a progressive, chronic condition influenced by multiple pathophys-

Table IV. Gold standards of medical therapy.

Disease/Indication	Gold Standard Therapy
Arterial thromboses (prevention)	Aspirin[66,69]
Breast cancer hormonal therapy	Tamoxifen[56]
Facial rejuvenation	Botulinum toxin[55]
Fungal infections	Amphotericin B[63,68,70]
GERD	Omeprazole[65]
Genital herpes	Acyclovir[57,62]
Juvenile rheumatoid arthritis	Methotrexate[60]
Migraine	Sumatriptan[58]
Parkinson's disease	Levodopa[59,67]
Scleroderma	Nifedipine[61]
Thrombolysis	Alteplase[64]

GERD = gastroesophageal reflux disease.

iologic mechanisms for which the treatment approach has changed with the introduction of new drugs (**Figure**).[71–75] Unlike glaucoma, GERD is a common disorder[76] and, even in its initial stages, produces symptoms that have a strong negative effect on QOL.[77] Throughout the 1980s, the treatment of choice for GERD included use of the H_2 histamine receptor antagonists, which purportedly gave the best symptom control, although a comprehensive review published in 1993 found that few randomized clinical trials showed improved healing or symptoms.[75]

In 1989, a new class of compounds appeared that suppressed gastric secretion by specific inhibition of the H^+/K^+ ATPase (proton pump) system at the secretory surface of the gastric parietal cell. The first of these proton pump inhibitors (PPIs) was omeprazole.[75] Evidence of the efficacy and safety of PPIs as the medical standard against which surgical therapy for uncomplicated esophagitis was compared,[72] and of the use of omeprazole as a cost-effective diagnostic test for noncardiac chest pain,[74] confirmed the validity of omeprazole's designation as the gold standard therapy for GERD (**Figure**).[71–75] Thus, despite the availability of alternative agents, omeprazole became recognized as the gold standard drug therapy because it reestablished expectations of treatment for GERD and was approved for a growing list of other indications.

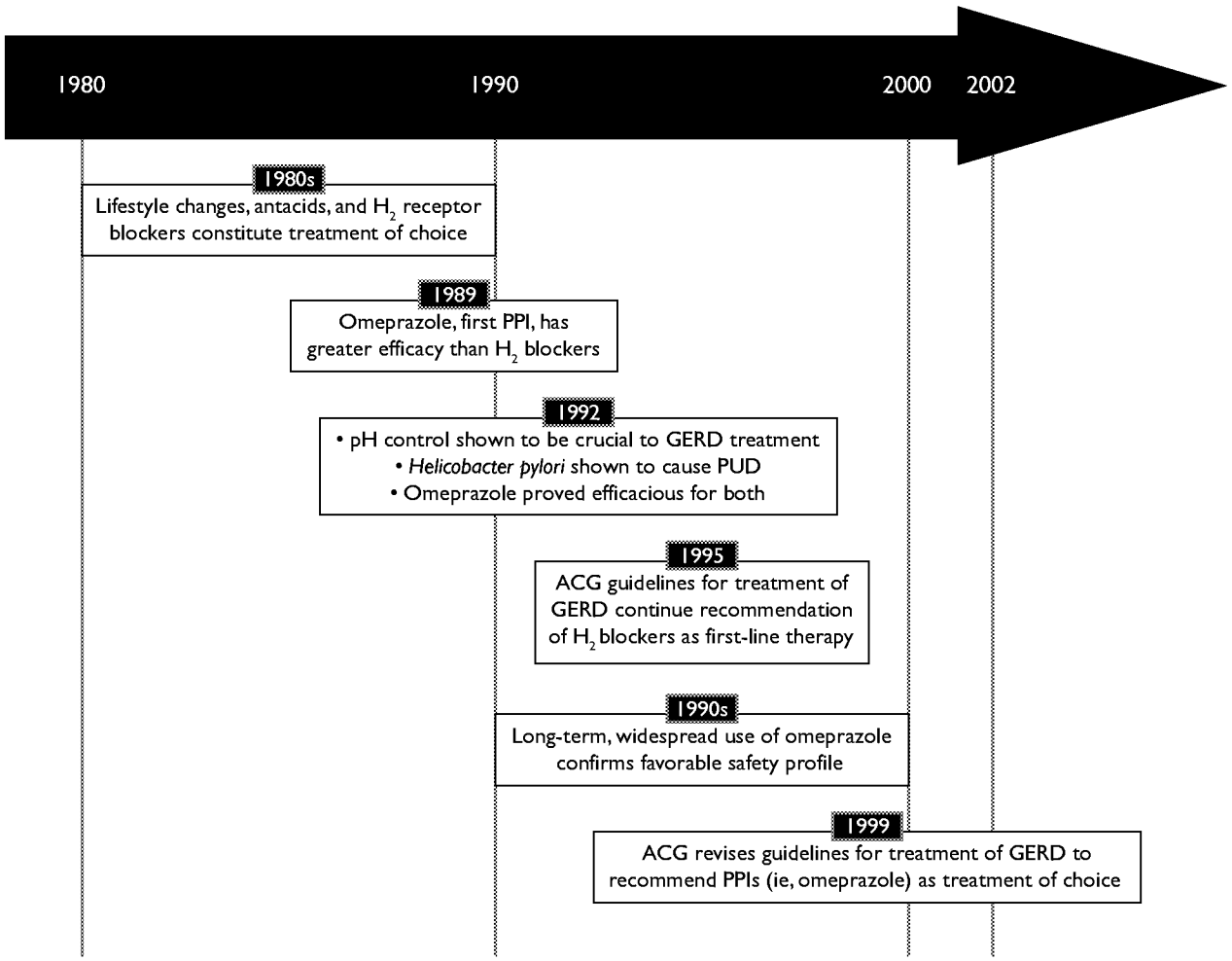

Figure. Evolution of a gold standard for gastroesophageal reflux disease (GERD).[71–75] PPI = proton pump inhibitor; PUD = peptic ulcer disease; ACG = American College of Gastroenterology.

Timolol for Primary Open-Angle Glaucoma

The nonselective beta-blocker timolol was approved for use as a topical ocular hypotensive agent in 1977.[78–80] Reducing IOP by suppression of aqueous humor production,[81] timolol was quickly recognized as a drug capable of providing effective IOP reduction, improved ocular tolerability, more convenient dosing, and excellent additivity with existing medications (eg, miotics) compared with other available topical agents used to treat glaucoma.[79,80] Improved tolerability and compliance, minimal ocular adverse effects (AEs), and applicability to all clinical types of glaucoma combined to increase its global use. First viewed as gold standard therapy for POAG in the early 1980s, timolol became the clinical benchmark in the majority of ocular hypotensive medication-registration trials. Clinicians worldwide have had >20 years of success with timolol.[82,83]

Although initial studies suggested that systemic AEs associated with timolol administration were mild and uncommon,[84] it is now clear that bradycardia,[85] lowered high-density lipoprotein cholesterol levels,[86] reduced pulmonary function,[87] and various psychiatric effects[88] are potential AEs of timolol therapy.[89] Other shortcomings, primarily with regard to long-term effectiveness in maintaining low IOP levels[90] and lack of uniform circadian reduction[91] in IOP, also became apparent. Topical prostaglandin derivatives, new alpha-adrenergic agonists, and topical carbonic anhydrase inhibitors were introduced in the mid-1990s. Given the arrival of these newer, safer, and effective treatments for reducing IOP, the gold standard status of timolol should be reassessed.

Gold Standard Designation: An Evolving Evidence-Based Process

From these examples, it appears that the process that drives the designation of gold standard status is evolutionary and ill defined. Ideally, a designation of *gold standard* should be based on an amalgamation of established criteria that reflect both pathophysiology and therapeutic goals. These criteria should be derived largely from an assessment of the outcomes of controlled trials published in the peer-reviewed literature. A rank assigned to each criterion is essential to represent the validity of outcomes and their relative importance to disease management.

Criteria for gold standards are dynamic. Periodic reassessment of the criteria and reconfirmation of designations of *gold standard* are essential. New scientific knowledge, such as the identification of a novel mechanism of action, may present opportunities for improving therapeutic interventions. New clinical data related to efficacy and safety also may highlight unmet needs.

PROPOSED CHARACTERISTICS OF GOLD STANDARD THERAPY FOR GLAUCOMA

The past and present treatment environments for POAG were discussed at the Vence meeting. The panel agreed that the choice of optimum medical therapy or a gold standard for disease management should be based on delivery of the greatest potential benefits in light of the level of risk and inconvenience acceptable to an individual patient.[10] Elements that constitute criteria for a gold standard medical treatment for glaucoma proposed by the panel are based on established therapeutic goals (**Table V**).

Table V. Criteria for a gold standard medical therapy.

Element	Criterion
Efficacy	Most effective IOP reduction, ability to achieve the desired target pressure range, IOP control over 24 hours, decreased potential for IOP fluctuations, and a long-term effect without inducing tachyphylaxis and tolerance
Safety	Lowest frequency and severity of AEs assessed over the long term
Compliance	Simplified medication regimen and minimal AEs
Widespread use	Acceptance by patients, physicians, and regulatory agencies that derives from a record of geographically broad, long-term use by a diverse patient population

IOP = intraocular pressure; AEs = adverse events.

Efficacy

Currently, IOP reduction is considered the most quantifiable therapeutic goal in the treatment of POAG. Both indirect and direct evidence substantiate this opinion. Incidence and prevalence, as a function of IOP, show that the risks for optic nerve damage[21,44,92,93] and visual field defect progression[92–95] increase as IOP levels increase. The risk of optic nerve damage increases with IOP, particularly in patients with IOPs >22 mm Hg compared with those with IOPs ≤15 mm Hg.[21] Similarly, direct evidence indicates that a reduction in IOP is associated with prevention of disease progression, protection of the optic nerve, and preservation of the visual field.[35,39,40,42,96–98] For example, in the Early Manifest Glaucoma Trial,[44] in which 255 patients were followed for a median of 6 years, glaucoma progression measured by perimetric and photographic optic disc criteria was strongly associated with the initial IOP reached after treatment or with no treatment. Each 1–mm Hg increase in IOP was associated with an estimated 11% increased risk.

At present, there is no way to precisely determine the IOP below which no further optic nerve damage will occur in a particular patient. In general, the initial goal is to lower the IOP by 20% to 30%.[42] However, a reduction >40% is justified in some severe cases of optic nerve damage or when other potential risk factors (eg, family and race) are present.[10] A prospective 10-year study of 90 patients showed that a current ocular hypotensive agent did not lower IOP sufficiently to preserve visual function.[99] Large multicenter trials have shown that IOP reduction with surgery or with combined medical therapies positively affects the course of disease progression.[38,39] The range of IOP levels and large diurnal fluctuations have also been found to be independent risk factors in patients with glaucoma and to promote the progression of visual field loss.[100–102] Consequently, the use of therapies that control fluctuations in IOP is warranted.

The choice of a reliable first-line therapy (ie, that is effective in both the short and long term in a diverse patient population) should be made carefully. Reports of patient response rates to currently available drugs vary widely (24% to 81%) and are a function of study criteria, including arbitrary IOP target end points, the severity of disease on study entry, and the known responsiveness of the patient's disease to treatment on enrollment.[90,103–106] Agents that may influence blood flow[107] and offer neuroprotection[108,109] may have potential in the treatment of POAG. Yet, at the present time, data are insufficient to substantiate an endorsement of these claims[19,107,109–114] in ameliorating glaucomatous functional impairment.

Efficacy: Current evidence suggests that the degree of IOP lowering is the principal factor in determining the most efficacious therapy. Preserving the visual field and protecting the optic nerve are generally considered consequences of reducing the IOP to an appropriate level (target pressure range) in an individual patient. The most effective IOP reduction, ability to achieve the desired target pressure range, IOP control over 24 hours, reduction of the potential for IOP fluctuations, and a long-term effect without inducing tachyphylaxis and tolerance should characterize the efficacy criteria for a gold standard medication.

Safety

When defining criteria to assess medical therapies, the anticipated benefit should be balanced against potential risks. The prevalence and severity of AEs associated with IOP-lowering agents need to be considered in relation to the potential effectiveness of the medication (risk-benefit ratio) and to the potential costs of treatment and/or hospitalization due to AEs.[115] Due to diverse mechanisms of action, the AE profiles of classes of ocular hypotensive agents differ. In particular, the systemic AEs prominent with the use of beta-blockers are not concerns with many of the new classes of ocular hypotensive agents. The beta-blockers, carbonic anhydrase inhibitors, cholinergics, and adrenergics are contraindicated in patients with specific comorbidities or may interact with other ocular or concomitant systemic therapies to diminish efficacy.[116] The use of topical beta-blockers, for example, is contraindicated in patients with a history of bronchial asthma, chronic obstructive pulmonary disease, sinus bradycardia, overt cardiac failure, or second- or third-degree atrioventricular block.[87,116–120] Although rare, the carbonic anhydrase inhibitor brinzolamide, if absorbed systemically, may produce an allergic reaction in patients who are allergic to sulfonamides.[116] The alpha-adrenergic agonist apraclonidine hydrochloride should be used with caution in patients with severe, uncontrolled cardiac disease.[121] The prevalence and severity of systemic AEs and the

occurrence of local AEs are important considerations in selecting a drug therapy.

Compared with published data on efficacy outcomes, AE reports are less standardized and frequently subjective.[122] There are several methodologic pitfalls in interpreting safety data, especially from uncontrolled clinical trials or cohort studies. First, the use of 2 different methods of obtaining AE data (spontaneous patient reporting and direct questioning) can introduce bias into collecting, reporting, and comparing prevalence among studies.[123] Patients are less likely to spontaneously report an AE than to report an AE when the practitioner solicits the information.[122,124] Unfortunately, study methodologies do not always describe how reports of AEs are gathered. Second, certain "expected" AEs, such as transient burning on the administration of an ophthalmic medication, may be neither volunteered by the patient nor elicited by the investigator. Thus, differing prevalences often are reported across studies. Third, methods of grouping and categorizing AEs vary by investigator. Finally, investigators rarely indicate when in the course of a study an AE is reported, making it difficult to distinguish between AEs that occurred at trial initiation and those that occur commonly throughout the study. In all, the clinical relevance of an association between a specific treatment and an adverse outcome depends on the strength of the evidence that supports the relationship. A full assessment of the likelihood of a causal relationship requires a systematic review of available evidence.[125]

Although few controlled trials are designed to study risk, postintroduction surveillance studies required by regulatory agencies in most countries help to establish the long-term safety profile of new medications. In addition, pharmacovigilance systems may be instituted to collect practitioners' postmarketing reports and determine the prevalence of AEs. However, the reliability of these data sets depends on the types of systems in place.

The severity of specific AEs often is reflected in therapy discontinuation rates. Sometimes clinicians assess the severity of AEs, consider the risk-benefit ratio, and decide whether a medication should be continued or discontinued or the dosing regimen should be changed. In other cases, persistency of use is determined by a patient's threshold for tolerating an AE. Compliance studies show that patients may stop using a medication for a multitude of reasons, including uncomfortable AEs, cost, and a lack of enthusiasm for using a medication on a routine basis.[126,127] Because tolerability influences medication compliance, it will eventually influence effectiveness.[127]

Safety: The local and systemic safety of glaucoma therapies should be considered as important as efficacy in the determination of a gold standard. The benefit-to-risk ratio is most positive with agents associated with the greatest reductions in IOP and the lowest frequency and severity of AEs assessed over the long term.

Compliance

Compliance is essential for successful glaucoma treatment. Because therapeutic regimens are initially preventive and the consequences of noncompliance are not immediately apparent, poor compliance remains a problem for many patients with glaucoma.[10,126,128,129] Although noncompliance has been reported in >50% of patients with glaucoma,[126,130] the inability to accurately assess noncompliance over the long term suggests that the true extent of the problem may not be fully realized.

Factors reported to affect compliance in patients with glaucoma include the patient's age and understanding of disease progression, tolerability, ease and frequency of dosing, and the cost to the patient of the medication.[116,125,131] Various strategies have been recommended to improve compliance with ocular therapy. Simplifying the medication regimen, particularly in terms of reducing the frequency and number of instillations per day, is one approach to enhancing compliance with glaucoma treatment regimens. Claxton et al[132] demonstrated that in a variety of medical disorders, compliance decreased as the number of daily medication doses increased. Similarly, therapies requiring instillation of ≥2 different agents per day not only increase the risk of additive AEs but also may be inconvenient for patients.[133]

Patient education is especially important in treating chronic, progressive diseases that have no immediate symptoms. Health care professionals other than primary care physicians may be integral in both determining the reasons for noncompliance and communicating or reinforcing relevant information (ie, the importance of using the medication as prescribed and adverse sequelae of their disease).[134,135] A common understanding among health care professionals is that

patients who understand their disease are more likely to be compliant with their medication regimens. Compliance with an ocular hypotensive dosage regimen is essential in preventing vision loss in later years.[136] Prescribers are aware that in certain countries and populations, medication costs can affect patient compliance.[131] Patients should be informed of the value provided by the course of treatment with an optimal therapeutic agent. When inferior medical therapy results in prolonged treatment and/or necessitates a change in the treatment modality (ie, surgical intervention), the true cost of medication increases well beyond the price of a daily dose.[137]

Compliance: The diversity of the glaucoma patient population encourages use of multiple approaches to enhancing compliance. A gold standard glaucoma medication should have a simple dosage regimen and minimal AEs to enhance compliance.

Widespread Use

Widespread use of a specific medical therapy for glaucoma is reflected in its applicability to a wide range of patients and its long-term acceptance by patients, physicians, and regulatory agencies. The breadth of applicability of a glaucoma therapy implies its versatility as an effective and safe agent in patients of different ages and races with various forms of the disease. In addition, an agent with wide applicability and limited contraindications can be used in patients with a broad range of comorbidities who are receiving other ocular or systemic medications. Acceptance by patients, physicians, and regulatory agencies is demonstrated by the extent of use, consistent and superior efficacy in reducing and maintaining reductions in IOP, a long-term safety record, and favorable tolerability and convenience. Although short-term experience is important, long-term follow-up of large cohorts is required to identify rare but serious AEs and tolerance to therapy.

Widespread use: Global applicability and widespread clinical experience are integral to the acceptance of any medication by patients, physicians, and regulatory agencies. Medications deserving of gold standard designation should have a record of geographically broad, long-term use by a diverse patient population.

Pharmacoeconomics

The burden of paying for glaucoma treatment falls primarily on third-party payers (private or governmental). Consequently, these payers closely evaluate glaucoma treatment patterns and their associated costs as they develop budget-impact analyses for their plans. The economic effects of various ocular hypotensive medications traditionally have been measured in terms of medication prices (acquisition costs) or medication costs per day.[138] Using either method, costs vary widely among therapies, and both methods fail to account for the major costs in glaucoma treatment.

Pharmacoeconomic analyses have been designed to take into account costs and clinical outcomes based on the general premise that the most expensive therapy is the one that does not work (ie, it allows disease progression and complications). Drug-acquisition costs of an effective therapy are often offset by decreased costs associated with reductions in disease progression and complications. Even expensive medications may be cost-effective if they are efficacious in treating a disease (ie, the effectiveness of an agent often outweighs its cost). A multinational study of patients with POAG or ocular hypertension found the primary contributors to the total cost of glaucoma treatment to be the initial IOP, the effectiveness of early treatment in reducing IOP, and the number of treatment changes because of the lack of efficacy or the occurrence of AEs.[139] In particular, a 3-week period associated with the date of treatment change was found to be an intense period when average daily costs increased 10- to 30-fold because of increased monitoring, consultations, testing, and sometimes surgery. The authors concluded that pharmacologic therapy for glaucoma that is effective, tolerable, and convenient should result in fewer treatment changes and, ultimately, in lower total costs.

Several studies have evaluated the impact of new pharmacologic therapies on surgery rates and, potentially, medical care costs. A survey of glaucoma treatment patterns in Scotland between 1994 and 1999 by Bateman et al[140] found that prescribing 3 new classes of ocular hypotensive agents (topical prostaglandins, carbonic anhydrase inhibitors, and alpha$_2$-agonists) increased by ~25% and that the number of trabeculectomies performed each year decreased by 46%. However, the investigators questioned whether the increase in prescribing prevented or only delayed the need for surgery.[140] In a separate study, in US patients diagnosed with glaucoma receiving Medicare,

the numbers of inpatient or outpatient glaucoma surgeries performed in 1999 were reduced by 72% and 42%, respectively, compared with 1994.[141] An analysis of quantitative changes in medical and surgical treatments of glaucoma in France between 1997 and 2000 found that the introduction of new ocular hypotensive agents, primarily latanoprost and brimonidine, was associated with improved IOP control and delayed surgery; the rate of surgery in patients receiving glaucoma-related medical treatment was reduced by 47% during the period.[142] These investigators estimated that 9500 fewer hospital days for anti-POAG surgical procedures were required in 2000 compared with 1997, resulting in a savings of €9.5 million (US ~$12.1 million).[142] This estimate needs to be refined in long-term studies of the economic effect of recent changes in glaucoma treatment strategies.

Medication cost is an important factor that varies widely from region to region. It is difficult, therefore, to designate a gold standard therapy that would meet the requirements of all patients, prescribers, regulatory agencies, and third-party payers.

Quality of Life

Patients with ophthalmologic diseases are at high risk for decreased functional status, which negatively impacts QOL.[143] Although various questionnaires have been devised to evaluate the effect of the disease and its treatment on QOL, reliable measurement tools are unavailable. Questionnaires such as the Medical Outcomes Study Short Form,[144] the Activities of Daily Vision Scale,[144] investigator-devised multidimensional instruments,[145,146] the National Eye Institute Visual Functional Questionnaire,[18] and the Short Form 36[18,147] have been used in clinical trials to measure outcomes in patients treated with medical and surgical therapies, the impact of glaucoma on QOL, and the relationship between visual problems and objective functional damage. For example, Perfetti et al[148] used a questionnaire of unspecified origin to evaluate QOL in patients treated at their Institute for Glaucoma. Of the 28% of 251 patients reporting a worsening of QOL, miotic therapies, polytherapies, and systemic therapies were the major exacerbating factors, primarily because of their dosing schedules and frequency. When the Activities of Daily Vision Scale was administered to 68 patients with glaucoma, increased field loss, decreased visual acuity, and complexity of the treatment regimen were correlated with reduced activities of daily living associated with vision (Spearman rank correlation; $P < 0.04$ for all comparisons).[144] Unfortunately, patients' perceptions of quality of vision measured via questionnaires seldom correlate with clinical tests of vision.[18,145–147] Therefore, better instruments are needed to enable clinicians to draw firm conclusions about the association between glaucoma and its treatment and a patient's assessment of QOL. Although impact on QOL should be considered when designating a gold standard therapy, currently available measurements do not allow for the outcomes of controlled clinical trials to be systematically evaluated.

DISCUSSION

Numerous therapeutic challenges exist in clinical glaucoma management. Foremost among these is the choice of therapy to prevent or halt optic nerve damage and preserve visual function. Evidence-based medicine has confirmed that lowering IOP is an important step toward this goal. Although different philosophies exist regarding the development of a long-term strategy for achieving adequate IOP reduction, medical therapy is usually chosen as the initial intervention.[149]

Criteria were proposed, at the Vence meeting, to define a gold standard medical therapy for POAG (**Table V**). There are no precedents for the current effort to identify a gold standard for POAG therapy. Although previously published biomedical consensus statements and practice guidelines may make general recommendations for procedures and tests or classes of equipment and therapeutic agents, there is a reluctance to promote individual products.[10,11] Nonetheless, rigorously defined standards can be valuable for a variety of reasons. First, gold standards inform the entire discipline. Evidence suggests that specialists follow practice guidelines more frequently than general practitioners and may, as a result, provide a higher quality of care for their patients.[150–153] A *gold standard* designation established with an evidence-based approach will have a broad impact on all ophthalmologic practitioners because the optimal therapy will have been distinguished from the usual annotated compendium of agents available to the general practitioner. The choice of a medication should

also be made in light of the needs of a particular patient. Second, the designation of *gold standard* often precedes a drug's acceptance as a benchmark. Gold standards and benchmarks can provide a necessary basis or reference for comparison in clinical trials. Third, the application of a gold standard therapy facilitates quality of care,[7,154] a key concern not only of patients and physicians but also of managed care professionals who see the link between quality and long-term cost reductions. A gold standard should not, however, be limiting, so that the choice of treatment will provide the greatest potential benefit in light of the level of risk, cost, and alterations in QOL acceptable to each individual patient.

An additional and significant challenge in clinical glaucoma management is the difficulty in monitoring disease progression. Direct measures of functional status are not yet sufficiently reliable or sensitive to guide the design of drug evaluation trials. Although many practice standards are created with incomplete knowledge of their impact on health and economic outcomes,[45,46] their adoption is considered appropriate because of the potential benefit to patients. Use of such imperfect standards may, however, lead to a miscalculation of the risk-benefit ratio and an increase in costs by encouraging the use of practices that have little value.[8] Fortunately, these concerns do not apply to the current effort. The potential benefit of IOP reduction in a setting where all other patient-specific factors are considered clearly outweighs any potential harm, and the concept of *gold standard* focuses, rather than broadens, practice patterns.

Eddy and Billings[8] have outlined the steps required to achieve high-quality medical care. First, evidence must be analyzed to develop standards that define the best practices. Second, existing practices must be evaluated with respect to the standards. Third, practitioners should adopt those practices that meet the standards. This article contributes to the first step in a larger effort to maximize the quality of care for patients with glaucoma. Criteria presented to evaluate IOP-lowering agents as gold standards include efficacy in reducing IOP and maintenance of effect, paucity of local and systemic AEs, promotion of patient compliance, and widespread use. These criteria should be employed to evaluate available and future medical therapies for glaucoma. The conceptual framework presented may be applicable to other therapeutic areas.

CONCLUSIONS

The public health liability imposed by vision loss for patients and health care systems domestically and internationally emphasizes the immediate need to identify a gold standard therapy for POAG. The present effort deserves the interest and involvement of the entire glaucoma community.

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