Photodynamic Therapy With Verteporfin

Observations on the Introduction of a New Treatment Into Clinical Practice

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Objective: To assess adherence to Food and Drug Administration–approved indications and Centers for Medicare & Medicaid Services policy through June 2001 regarding the use of photodynamic therapy in Medicare beneficiaries.

Design: Systematic review of pretreatment fluorescein angiograms of 1245 consecutive Medicare patients who received photodynamic therapy from physicians in 3 contiguous Medicare coverage areas (fee-for-service arrangement) and in 136 consecutive patients in a Medicare health maintenance organization.

Results: In the 3 Medicare fee-for-service regions, payment denial due to nonconforming fluorescein angiograms ranged from 17% to 29% by region in 1245 beneficiaries. In the health maintenance organization setting, 60 (44%) of 136 submitted angiograms were nonconforming, including 8 in which the photographic quality was too poor to grade the lesion size, composition, or both.

Conclusions: A substantial proportion of the actual or intended clinical application of photodynamic therapy with verteporfin was directed to patients who did not meet concurrent published clinical criteria associated with treatment benefit or national coverage policy. Although this policy has evolved, it still depends on fluorescein angiographic interpretation, suggesting that there is an opportunity to improve the cost-effectiveness of delivery of photodynamic therapy with verteporfin to Medicare beneficiaries.


On April 12, 2000, the Food and Drug Administration (FDA) approved a new drug, verteporfin, to be used in photodynamic therapy (PDT) in selected cases of age-related macular degeneration (AMD). The advanced stage of AMD is the leading cause of blindness in people older than 55 years in the United States, with approximately 1.3 million new cases in this age group expected between 2000 and 2005. Much of the blindness from this disease is caused by the growth of aberrant blood vessels, termed choroidal neovascularization (CNV), from the capillaries of the choroidal circulation. Choroidal neovascularization usually develops under the macula, in the center of the retina, and is typically accompanied by bleeding and fibrovascular proliferation that results in disruption of the function and architecture of the macula’s photoreceptors, causing severe loss of central vision.

Laser photocoagulation has been the standard treatment for CNV that does not extend under the center of the macula since 1982, when randomized clinical trials confirmed that such treatment reduced the risk of severe vision loss compared with no treatment. However, this treatment can destroy not only CNV but also any functioning retinal tissue overlying the CNV, and it is not beneficial for most cases of CNV that extend under the center of the macula.

In PDT, intravenous verteporfin is infused for 10 minutes, concentrating in the neovascular tissue. As a photosensitizer, the drug can be activated by a low-intensity laser light and can cause selective damage to fibrovascular tissue without damaging overlying functional retinal tissue. Clinical trials have shown that this therapy can reduce the risk of moderate and severe visual acuity loss in selected cases of CNV that extend under the center of the retina.

Initial FDA approval of this drug was based on the results of 2 of these randomized clinical trials. At 1 year, 39% of verteporfin-treated eyes had lost at least 3 lines of visual acuity compared with 54% of control eyes. However, this treatment ben-
efit was not observed for all subjects who met the entry criteria of having subfoveal CNV and some evidence of classic CNV on fluorescein angiography. Instead, benefit in this trial seemed to be limited to patients whose CNV, when imaged on fluorescein angiography, had a pattern of fluorescence termed predominantly classic (the area of classic CNV was >50% of the area of the entire lesion), as determined in a masked manner subjectively by experienced graders at a central fluorescein angiogram reading center. No statistically significant treatment effect was seen for patients with a minimally classic angiographic pattern of fluorescence (the area of classic CNV was <50% of the area of the entire lesion). On the basis of the study findings, FDA approval and subsequent Medicare payment policy was limited to treatment of patients with a predominantly classic fluorescein pattern. Subsequent analyses, based on 2 years of follow-up, showed that the treatment effect was sustained. More recent information, available at the time this study was nearing completion, indicated that PDT with verteporfin could reduce the risk of moderate and severe vision loss in patients with an occult lesion with no classic composition. This seemingly contradictory information suggested that therapy was beneficial for predominantly classic and occult fluorescein patterns with no classic lesions but not for minimally classic lesions. However, additional analyses suggest that other factors, such as the size of the lesion associated with these different angiographic patterns, might account for some of the various outcomes noted in the subgroup analysis of angiographic patterns. In January 2004, these findings were used in a national coverage analysis by the Centers for Medicare & Medicaid Services (CMS) to update its coverage policy to include relatively small occult fluorescein patterns with no classic lesions and minimally classic lesions with recent disease progression. Even with these revisions to coverage, determining which lesions are included in the coverage policy still requires expertise in fluorescein angiographic interpretation. After dilated ophthalmoscopy, patients suspected of having CNV usually undergo fluorescein angiography to determine whether laser photocoagulation or PDT with verteporfin should be considered. The effects of either form of treatment are monitored by clinical assessment and subsequent fundus photography and fluorescein angiography, with additional therapy considered if leakage of fluorescein from CNV is noted. When additional therapy was applied in this way in the clinical trials of PDT with verteporfin, patients received a mean of 5 to 6 courses of treatment in 2 years.

The treatment is expensive. Total mean costs, using 2001 Medicare-allowed charges, for 4 treatments and associated examinations every 3 months for 2 years (ie, 8 physician examinations, 8 color fundus photographs, 8 fluorescein angiograms, 4 vials of the drug, and 4 applications of laser to activate the drug) are approximately $12 300 per patient. Approximately 40% of this cost is for the drug alone.

In the field of ophthalmology, the introduction of a new treatment for a leading cause of blindness was a major event. For investigators interested in health services research and the assessment of new medical technologies, the approval of PDT for AMD offered a window into the adoption and use of a new treatment in the Medicare population. The requirement to perform fluorescein angiography as a prelude to treatment and the specific angiographic criteria associated with Medicare coverage afforded us a unique opportunity to examine the introduction into medical practice of this new treatment coupled with angiographic criteria.

METHODS

In 4 geographic regions of the United States, we systematically reviewed the fluorescein angiograms of 2 groups of patients with subfoveal CNV associated with AMD: those who had received PDT with verteporfin treatment and those who had been recommended for treatment pending payer approval. Three of the 4 locations were contiguous Medicare coverage regions that served approximately 850 000 Medicare beneficiaries. Physician payment for this population was based on the standard Medicare fee-for-service arrangement. In these regions, the Medicare medical director (P.P.), a practicing ophthalmologist, published reimbursement criteria for PDT that indicated that all initial fluorescein angiograms would be reviewed and that payment for PDT would be based on fluorescein angiographic documentation of predominantly classic CNV in patients with AMD. Between April 1, 2000, and May 31, 2001, the Medicare medical director requested copies of the fluorescein angiograms of all patients undergoing initial PDT with verteporfin; he reviewed the submitted angiograms personally using published guidelines to determine whether they demonstrated AMD with a predominantly classic pattern. Angiograms were submitted as positive transparencies or as positive prints by 35 different ophthalmologists. Angiograms that were difficult to interpret or that were disputed were sent in a masked manner (ie, with no patient identifier and no indication of the original interpretation) to the Wilmer Eye Institute for interpretation by an expert in AMD and PDT with verteporfin (N.M.B. or other ophthalmologists who had participated in the photograph reading center for the TAP [Treatment of Age-Related Macular Degeneration With Photodynamic Therapy] investigation). Each angiogram received a final designation of “showing predominantly classic CNV” (ie, evidence of treatment benefit), “not showing predominantly classic CNV,” or “cannot grade lesion composition” (eg, owing to inadequate photographic quality). The Medicare database recorded information on final payment status for the treatment (ie, approved or denied). Only data related to the first treatment for each patient were considered (April 1, 2000, through May 31, 2001).

The fourth location for this evaluation involved a Medicare population enrolled in a health maintenance organization (HMO) with a Medicare contract that served approximately 35 000 beneficiaries. In this setting, the HMO medical director informed participating ophthalmologists that pretreatment review of all patients proposed for PDT with verteporfin would be mandated. All retinal angiograms were sent by an express courier to the Wilmer Eye Institute, where standardized interpretations were performed within 48 hours by an expert in AMD and PDT with verteporfin (N.M.B. or other ophthalmologists who had worked at the photograph reading center for the TAP investigation). Each angiogram was graded according to whether it met angiographic eligibility criteria for PDT at the time of grading (“no,” “questionable,” “yes,” or “cannot grade”). In 2001, data became available indicating that there was potential treatment benefit for some patients with occult lesions but not classic lesions in whom recent disease progression was assumed. Patients with such angiographic evidence were also graded “yes.”
The **Table** gives the rates of agreement with the diagnosis of predominantly classic CNV resulting in reimbursement or payment denial for the 3 Medicare fee-for-service regions during the 14 months of the program. Payment denial rates, which were not statistically significantly different by location, ranged from 17% to 29% among 1245 patients. During the 14 months of observation, there were no clear time trends in denial rates. Table 1 also summarizes the interpretation of the retinal angiograms submitted by the Medicare HMO ophthalmologists during a 2-year period. In this setting, treating physicians were required to obtain preapproval before delivering PDT. The angiograms of 136 patients were reviewed. Sixty-three (46%) of these patients had retinal angiograms that showed a lesion that met the criteria for PDT as defined previously herein, 13 (10%) had angiograms that probably (graded “questionable”) met these criteria, 52 (38%) had angiograms that showed a lesion that did not meet these criteria, and 8 (6%) had retinal photographs of inadequate quality to grade the lesion composition.

It is rare to have the opportunity to evaluate the uptake and application of a new medical treatment into clinical practice in which FDA approval and physician reimbursement policy are based on specific results or interpretation of a single diagnostic test. Treatment of AMD with verteporfin afforded such an opportunity. This evaluation found that approximately 20% to 40% of planned or actual treatments did not meet the concurrently recommended or allowed guidelines for treatment. This difference in interpretation and potential impact on treatment benefit raises many questions.

Many possible factors may contribute to this study’s findings, including difficulty with angiographic interpretation, misunderstandings related to the application of angiographic interpretation to clinical practice, physician incentive, and patient demand. The latter 2 factors may be influenced by the lack of other effective treatments for this potentially blinding disease. Potential barriers to physician acceptance and adherence to clinical guidelines are numerous. In the case of fluorescein angiography, the challenges of standardization of angiographic interpretation are recognized. In a clinical trial of neovascular AMD, the proportion of patients subsequently found not to meet angiographic eligibility for the trial, based on retrospective review by a central reading center, was at least 10%. A recent publication from Europe reported substantial intraobserver and interobserver variability among retinal specialists grading the pattern of CNV based on only high-quality digital angiograms of patients with known CNV.

Differences in angiographic interpretation could lead to substantial excess costs for payers such as Medicare. It is estimated that approximately 260,000 people in the United States each year experience new loss of central vision from advanced AMD and that approximately two thirds of these cases, or approximately 175,000, will be due to CNV (the other third lose vision because of atrophy in the center of the macula). If 50% of the neovascular cases have evidence of classic CNV and 40% of those
lesions are predominantly classic (as was noted in clinical trials that enrolled patients who had lesions with any proportion of classic CNV), approximately 35000 patients annually in the United States will develop a new CNV lesion that is predominantly classic. If all 35000 patients received the 2 years of treatment and related follow-up as in the original trials, the estimated 2-year cost for this 1-year cohort of new cases, using current Medicare reimbursement, is more than $400 million. On the basis of the experience reported in this evaluation, we estimate that an additional 8750 patients (ie, 25% of 35000) with AMD had therapy that may not have been beneficial or met the criteria for coverage by Medicare, at a 2-year cost of approximately $100 million to Medicare and other payers. Even if some of these cases actually would have met the criteria for which therapy is currently covered, the new coverage analysis still depends on angiographic criteria. If misinterpretation occurs of angiograms presumed to show relatively small occult lesions with no classic or minimally classic lesions, additional patients with AMD during the next several years may have therapy that may not be beneficial or meet the criteria for coverage by Medicare (eg, a large minimally classic lesion interpreted as a small lesion). If such interpretation applies to approximately 8750 patients, the situation could result in approximately $100 million of potentially unnecessary cost to Medicare and other payers.

How can the costs of likely nonbeneficial treatments be minimized? Health care costs have increased dramatically in recent years, and cost escalation has been particularly large for Medicare beneficiaries, who use a substantial share of health care resources, especially those associated with new treatments for chronic diseases. Although there is broad interest in developing local and national strategies to contain costs without compromising quality of care, our experience suggests that trying to use and sustain focused strategies is problematic and may offer some insights into obstacles and opportunities associated with efforts to improve cost-effectiveness in this and analogous new treatments.

First, there may be an opportunity for improvement in the education of physicians in the interpretation of fluorescein retinal angiograms specifically as they relate to treatment effectiveness for this condition. In the application of PDT, the criteria for approval of and payment for an expensive treatment have been determined based on the context and results of rigorously controlled clinical trials; however, these trial results cannot be extrapolated reliably to clinical practice. Studies would need to demonstrate that such educational opportunities could result in more uniform interpretation, perhaps using a central photograph reading center as a standard for such studies. Most continuing medical education courses on AMD and PDT discuss results of the trials but do not concentrate on the details of fluorescein angiographic interpretation of lesions, as was described in the 1990s by the Macular Photocoagulation Study Group and more recently by investigators participating in PDT trials. In clinical trials related to AMD, substantial efforts have been devoted in recent years to the establishment of independent photographic reading centers. Much of the logic underlying the development of such centers is the recognition that reproducible interpretation of fluorescein angiography is difficult to achieve in a clinical setting. Generalizability is always a concern in trying to apply the results of a clinical trial to practice, typically because the inclusion criteria necessary for participation in practice-based studies of effectiveness of new interventions do not accurately represent the full target population for the treatment after approval. However, the problem is different in the case outlined herein. The inclusion criteria for the PDT trials were not restrictive; the problem seems to lie in misclassification of lesion size or lesion composition on fluorescein angiography, the major determinants currently for deciding which patients should be offered the treatment.

Second, an approach to improving cost-effectiveness could be to evaluate outcomes with and without a utilization program similar to that described in this article. This would seem self-evident and an important potential role for academic medical centers performing clinical trials that also have an interest in the subsequent use of the interventions they study. However, although the CMS has a mandate to write coverage policy, Congress has given it almost no tools to establish or improve the cost-effectiveness of how its coverage policy is actually applied. It seems ironic that the CMS, the largest source of health care insurance in the United States and the primary insurer for almost everyone with AMD, is organizationally limited by Congress regarding its ability to improve utilization. Most Medicare beneficiaries obtain their care through a traditional, fee-for-service model. The CMS has no authority to perform any type of pretreatment assessment (ie, an external review of a fluorescein angiogram before treatment). It can only perform posttreatment, prepayment reviews. This is an awkward and inefficient strategy to try to improve the utilization of services. First, the treatment and its costs to the provider and patient have been incurred at the time of the review, and the treatment’s risks have already been experienced. Second, the CMS has only a limited ability to do such reviews owing to bureaucratic restrictions on its ability to request records from providers in a systematic way. In contrast, an HMO that contracts with the CMS for care of Medicare beneficiaries may put into place a variety of prospective utilization review procedures to support its coverage policy. In the case of PDT with verteporfin, external review of fluorescein angiograms has been effective in assisting in the confirmation of patients who might benefit from the therapy and in the education of the physicians regarding fluorescein angiographic interpretation.

Prospective utilization review as described in this article may be particularly effective for PDT because it is based on objective criteria (albeit requiring subjective interpretation of a diagnostic image) rather than on the interpretation of a constellation of signs and symptoms from a medical record review. Furthermore, the knowledge that a review of some or all of the fluorescein angiograms was occurring might increase a physician’s scrutiny regarding which cases might be considered for therapy. In the settings described in this article, all of the treating physicians were aware that the angiograms were being re-
viewed. It is therefore possible that the rate of nonconforming angiograms in an unsurveilled population would be larger.

In the case of PDT with verteporfin, the approach of using an external center to review use of this service benefited from several specific circumstances. First, treatment coverage is based on a single diagnostic test; second, it is possible to interpret fluorescein angiograms and provide a report rapidly enough so as not to affect the provision of optimal patient care; and third, the angiographic interpretation was authoritative and was identical to that used in the clinical trials that initially demonstrated the effectiveness of the treatment. A flexible appeals process is still required to recognize the possibility of borderline interpretations, insufficient photographic quality, and variability in interpretation as well as incorporation of new information that could precede policy changes (as was done for the Medicare beneficiaries in the HMO in this study because new information resulted in a change in guidelines regarding treatment indications). The use of external, impartial centers to review utilization and the findings of our evaluation also raise the issue of local vs national policies for Medicare’s coverage of new technologies and treatments. During the period of our evaluation, the locations surveilled were subject to a far more rigorous utilization review than were other regions of the country.

As argued effectively by Foote, variation in local policy is self-evident. On the other hand, Medicare has historically and politically reasons, the CMS does not overtly associate with access, or not, to a new treatment or to evidence-based medicine?).

The initial introduction of PDT provides an example of the mismatch that may occur among numerous reviews that have different purposes, including FDA approval, CMS coverage policy, evidence of treatment benefit in the peer-reviewed literature, preferred practice patterns, and actual practice. Is PDT with verteporfin a unique example of a new treatment for which clinical indication can or should be limited to populations that can be clearly defined? Is its potential misapplication rate unique? Probably not; other medical treatments or devices may be analogous (ie, in which evidence exists for expertise in test or image interpretation), such as biventricular pacemakers, new pharmacologic agents for the treatment of sepsis, and thromboses. Congress has given the CMS authority to set coverage policy, to police fraud, and to perform limited nonsystematic reviews of treatments after they have been provided. There is a huge, unexplored potential to improve the cost-effectiveness of existing and future coverage policies, particularly for new technologies and treatments as they are introduced. For historical and political reasons, the CMS does not overtly consider cost-effectiveness in its coverage policy. It seeks to follow the directive of Congress to cover what is “reasonable and necessary,” but it has not established written rules regarding this directive because of the efforts of interest groups. The desire to cover only effective treatments is self-evident. On the other hand, Medicare has tried to control escalating health care costs by simple reduction of payment to health care professionals, hospitals, and other medical facilities. In the current environment of escalating health care costs, the uncoupling of effectiveness and cost containment is neither sensible nor sustainable. These problems and the opportunities they bring are not unique to the CMS. All payers of health care are faced with the challenge of developing policies regarding which treatments to cover and, with the paucity of effective strategies, matching and limiting effective treatments to those likely to benefit. Physicians as a group also do not benefit from the overuse of expensive drugs. The total cost of each verteporfin injection to Medicare in 2002 was approximately $1400. Drug companies and device manufacturers are paid for their products regardless of whether the CMS or its contractors determine that the treatment meets payment guidelines. The expense of drugs and devices exerts downward pressure on the conversion factor used by the CMS to set its annual payment to physicians for a particular service.

The processes described in this article represent an effort by an academic medical center, practicing physicians, a contracted adjudicator for the CMS, and a private health insurance company to provide an expensive new treatment to the group of patients it was scientifically proved to benefit instead of to all patients to whom the treatment might be offered. Such collaborations related to the provision of certain health care treatments, especially those involving new, expensive technologies, have the potential to offer benefit to patients, health care professionals, payers of health care, and society.

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REFERENCES


Correction

Misspelled Surname. In the Clinicopathologic Reports, Case Reports, and Small Case Series article by Beck et al titled “Is Coxackievirus the Cause of Unilateral Acute Idiopathic Maculopathy?” published in the January 2004 issue of the ARCHIVES (2004;122:121-123), the third signature should have read as follows: David A. Glaser, MD, Florissant, Mo.
uously with grid laser photocoagulation are not eligible for study participation. Study subject enrollment is expected to begin in June 2004. Additional information about study subject eligibility criteria and the SCORE Study can be found online at http://spitfire.emmes.com/study/score/.

The SCORE Study has the potential to either demonstrate the efficacy and safety of an unproven treatment for macular edema associated with CRVO and BRVO or to demonstrate that a commonly performed treatment is not effective or safe in the long-term. Meeting the study enrollment goal is critical to achieving the scientific objectives of the study. Since only a randomized, controlled clinical trial can provide us with the best information needed to determine the safety and efficacy of intravitreal triamcinolone compared with standard care at this time, ophthalmologists should consider referring individuals who are possibly eligible for the SCORE Study to a SCORE Study clinical investigator for potential inclusion in this important study. For a list of clinical investigators in your area, please visit the SCORE Study Web site or call (301) 251-1161.

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Correction

Error in Table. In the article titled “Photodynamic Therapy With Verteporfin: Observations on the Introduction of a New Treatment Into Clinical Practice,” published in the January issue of the ARCHIVES (2005;123:58-63), there was an error in the Table. In the section labeled “Medicare Fee-for-Service Settings,” the final column heading should have read “Denied, No. (%)‡,” and the numbers underneath should have been “242 (19).” The ARCHIVES regrets the error.