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Cost-Effectiveness of Fluocinolone Acetonide Implant Versus Systemic Therapy for Non-infectious Intermediate, Posterior and Panuveitis

Elizabeth A. Sugar, PhD^{1,2,3,4}, Janet T. Holbrook, PhD, MPH^{2,3}, John H. Kempen, MD, PhD^{5,6,7}, Alyce E. Burke, MPH^{2,3}, Lea T. Drye, PhD^{2,3}, Jennifer E. Thorne, MD, PhD^{2,8}, Thomas A. Louis, PhD¹, Douglas A. Jabs, MD, MBA^{2,9,10}, Michael M. Altaweel, MD¹¹, Kevin D. Frick, PhD¹², and The Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group*

¹Department of Biostatistics, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland ²Department of Epidemiology, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland ³Center for Clinical Trials, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland ⁴Division of Biostatistics and Bioinformatics, The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD ⁵Ocular Inflammation Service, Department of Ophthalmology/Scheie Eye Institute The University of Pennsylvania, Philadelphia, Pennsylvania ⁶Center for Preventive Ophthalmology and Biostatistics, Department of Ophthalmology/Scheie Eye Institute, The University of Pennsylvania, Philadelphia, Pennsylvania ⁷Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, The University of Pennsylvania, Philadelphia, Pennsylvania ⁸Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland ⁹Department of Ophthalmology, The Icahn School of Medicine at Mount Sinai, New York, New York ¹⁰Department of Medicine, The Icahn School of Medicine at Mount Sinai, New York, New York ¹¹Fundus Photograph Reading Center, Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, Wisconsin ¹²The Johns Hopkins University Carey Business School, Baltimore, Maryland

Abstract

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Corresponding Author: Elizabeth A. Sugar, PhD; Department of Biostatistics; the Johns Hopkins Bloomberg School of Public Health; 615 North Wolfe Street, E3537; Baltimore, MD, 21205; esugar@jhsph.edu **Reprint Requests:** Douglas A. Jabs, MD, MBA; MUST Chairman's Office; Department of Ophthalmology; Icahn School of Medicine at Mount Sinai; One Gustave L. Levy Place, Box 1183; New York, New York 10029-6574; douglas.jabs@mssm.edu.

*The Credit Roster for the Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group appears in Appendix 1 available at www.aaojournal.org

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Supplemental Material: This article contains online-only material. The following should appear online-only: Tables 1 and 2, and Appendix 1.

Objective—To evaluate the 3-year incremental cost-effectiveness of fluocinolone acetonide implant versus systemic therapy for the treatment of non-infectious intermediate, posterior, and panuveitis.

Design—Randomized, controlled, clinical trial.

Participants—Patients with active or recently active intermediate, posterior, or panuveitis enrolled in the Multicenter Uveitis Steroid Treatment Trial.

Methods—Data on cost and health-utility during 3 years post-randomization were evaluated at 6-month intervals. Analyses were stratified by disease laterality at randomization (31 unilateral vs 224 bilateral) due to the large upfront cost of the implant.

Main Outcome Measures—The primary outcome was the incremental cost-effectiveness ratio (ICER) over 3 years: the ratio of the difference in cost (in United States Dollars) to the difference in change in quality adjusted life years (QALYs). Costs of medications, surgeries, hospitalizations, and regular procedures (e.g. lab monitoring for systemic therapy) were included. QALYs were computed as a weighted average of EQ-5D scores over the 3 years of follow-up.

Results—The ICER at three years was \$297,800/QALY for bilateral disease, driven by the high cost of implant therapy (Difference Implant – Systemic []: \$16,900, $p < 0.001$) and the modest gains in QALYs (= 0.057, $p = 0.22$). The probability of the ICER being cost-effective at thresholds of \$50,000/QALY and \$100,000/QALY was 0.003 and 0.04, respectively.

The ICER for unilateral disease was more favorable, \$41,200/QALY at 3 years, due to a smaller difference in cost between the two therapies (= \$5,300, $p = 0.44$) and a larger benefit in QALYs with the implant (= 0.130, $p = 0.12$). The probability of the ICER being cost-effective at thresholds of \$50,000/QALY and \$100,000/QALY was 0.53 and 0.74, respectively.

Conclusion—Fluocinolone acetonide implant therapy was reasonably cost-effective as compared to systemic therapy for individuals with unilateral intermediate, posterior or panuveitis but not for those with bilateral disease. These results do not apply to the use of implant therapy when systemic therapy has failed or is contraindicated. Should the duration of implant effect prove substantially longer than three years or should large changes in therapy pricing occur, the cost-effectiveness of implant versus systemic therapy would need to be re-evaluated.

Keywords

adalimumab; azathioprine; cyclosporine; cyclophosphamide; daclizumab; infliximab; methotrexate; mycophenolate mofetil; rituximab; tacrolimus

The Multicenter Uveitis Steroid Treatment (MUST) Trial was designed to compare the effectiveness of systemic administration of oral corticosteroids (and immunosuppressive drugs where indicated)¹ versus fluocinolone acetonide implant therapy (which is surgically implanted in the patient's eye and releases corticosteroid into the eye over time)^{2,3} for the management of active or recently active intermediate, posterior and panuveitis. Fluocinolone acetonide implant treatment is characterized by high up-front costs (the implant itself and the surgical costs to implant) followed by limited costs until the device needs to be replaced. In contrast, systemic therapy needs to be administered continuously until the disease becomes quiescent. Once the disease is controlled, therapy may either be continued or halted

and renewed upon re-activation unless the disease remits. This results in a lower up-front cost than the implant but the expectation of higher ongoing expenditures thereafter.

Although cost is an important factor in medical decision making, it is important to examine both cost and efficacy to determine which therapy will have the best value⁴. A cost-effectiveness analysis makes the tradeoffs between greater costs and greater effectiveness explicit. An analysis that uses a general health-related quality of life metric such as the EQ-5D⁵ to evaluate treatment efficacy is preferred since it is comparable across all disease types⁶. The choice of treatments is straightforward when the better treatment is less expensive. However, a cost-effectiveness analysis is particularly useful when the more expensive therapy is more effective in improving health utility, as in the MUST Trial⁷, since it addresses the important question of whether the additional expenditures needed to achieve the extra health improvements are worthwhile. Here, we report a formal incremental cost-effectiveness analysis for the MUST Trial, estimating the incremental cost per quality adjusted life year (QALY) gained by using implant therapy as compared to systemic therapy.

Methods

Details of the MUST Trial ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00132691) identifier NCT00132691) have been described previously^{7,8}. The institutional review boards for all centers approved the protocol and all participants provided written informed consent. The methods involved in converting cost and effectiveness information into a cost-effectiveness analysis include: (1) ascertaining what resources were used in each treatment group over time and assigning prices to each of these; (2) prospective measurement of health utility over time; (3) statistical analyses to produce estimates of the incremental costs and incremental quality-adjusted life years (QALYs); (4) calculating the ratios of the incremental values and the variability of those estimates; and (5) sensitivity analyses to assess the impact of assumptions made in the above analyses.

Utilization and Cost Data

Costs were calculated based upon prospectively collected data on health care utilization records using the patient as the unit of analysis, which is concordant with the patient-level randomization for the MUST trial. Patients who died during the study were assigned a cost of \$0 for all remaining study visits. The sources of data and the methods of placing a value on each resource are described below.

All physician and laboratory procedures were assigned a cost based on the Medicare reimbursement rate for the Current Procedural Terminology (CPT) code⁹. The cost of the implant was treated as the average wholesale price of the implant itself (\$21,900) plus the physician fee (\$835), the Medicare national average facility fee for the procedure (\$1,654) and the anesthesia fee (\$189)^{10,11} if necessary. The national average price for implant removal was \$891. When multiple surgeries were performed simultaneously those beyond the first were discounted as per Medicare payment protocol¹². Hospitalizations were assigned a cost based on the number of days in the hospital and the average charge for a hospital day (\$1,853 per day).

The use of local and systemic medication to treat uveitis was recorded prospectively for both groups. Data on non-uveitis medications were also collected. The specific medication and daily dosage information was collected on study forms for oral corticosteroids. For other medications, the relevant utilization information was determined using the following procedure. First, any class of medications that were used by two or fewer study participants was excluded as idiosyncratic utilization that would not accurately inform average utilization. We assumed that medications were taken for the entire interval between two visits if the drug was noted at both visits and for half of the interval if the drug was only noted at one of the two visits bounding the interval. The dose, strength, and frequency were estimated from the starting doses identified in literature providing guidelines¹ for treatment and utilization patterns reported in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study¹³ with consultation from study clinicians where necessary. Specific exceptions to these rules include intraocular injections (e.g., bevacizumab), drugs for migraines, sleep aids, narcotics and antibiotics. In these cases, specific algorithms were based on the drug's particular utilization patterns. For example, antibiotics were assumed to be used for a single 10 day course of treatment. All drugs were assigned a cost based on the average wholesale price from the *Red Book of Drug Topics*¹⁴.

Effectiveness Data

The effectiveness measure for health utility was calculated from the EQ-5D questionnaire⁵ administered prospectively during biannual interviews with study participants. This questionnaire includes a total of five questions (one each for pain, anxiety/depression, mobility, usual activities, and self-care [activities of daily living]). For each question, the participants answer that they have essentially no problem, a moderate problem, or a severe problem in that domain. Health utility values are derived from the responses using a validated algorithm derived from responses of a representative sample of individuals in the United States regarding their willingness to make tradeoffs between different health states¹⁵. Scores range from -0.11 to 1.0, where 1 represents perfect health (i.e., no problem for all five domains), 0 is equivalent to death, and negative scores represent health states worse than death. Study participants who died were assigned a utility of zero for all subsequent visits, rather than treating these observations as censored or missing. This approach is intended to provide a common metric in which the impacts of morbidity and mortality are captured.

Time Horizon

The primary MUST trial was designed with high power for outcomes at 24-months; however, the effects of the fluocinolone acetonide implant last at least three years in most cases³. Thus, we conducted the cost-effectiveness analysis based on bi-annual visits using a three-year time horizon.

Perspective for Economic Analyses

We used the payer's perspective for costs and the patient's perspective for outcomes. The result of using this combination of perspectives indicates how much more it would cost a

payer to improve the health of uveitis patients by using the more effective and more costly treatment.

Statistical Analysis

Analyses were conducted according to randomized treatment and were stratified by the number of eyes with uveitis at enrollment (unilateral [$N = 31$] versus bilateral disease [$N = 224$]). The primary analysis estimated the excess money spent (in United States [US] dollars) per quality adjusted life year (QALY) gained for the implant versus the systemic treatment groups at three years. Generalized estimating equations (GEE) with robust standard errors were used to obtain parameter estimates for longitudinal models of cost and QALYs.

The costs of the treatments were aggregated at the individual level for each six month interval to correspond to the points where utilization measures were obtained for all individuals. Linear regression with a saturated means model was used to determine the difference in average total cost between the two groups. Costs were then aggregated to the year and down-weighted (i.e., discounted) 3% per year in years 2 and 3 (i.e. dividing by 1.03 and 1.03², respectively) based upon the recommendation of the US Panel on Cost-Effectiveness in Health and Medicine⁶. A working independence covariance structure was used to account for longitudinal within-person correlation.

We assumed that both groups' health utilities would have followed the same trajectory if it were not for the intervention. Based upon that assumption, we estimated the difference between groups in the mean change in QALYs experienced over three years. Changes in health utility were estimated using a saturated means model and an exchangeable longitudinal correlation structure. Health utility was converted into QALYs by accounting for the time each observation was assumed to apply. For the observations at the transitions between years 1 and 2 and years 2 and 3 (i.e. year 1, 2 and 3 measurements) a weight of 0.25 was assigned to both the prior and subsequent years, for a total input of 0.50. All intermediate observations (i.e. at 6, 18, and 30 months) received weights of 0.50. As with the costs, a 3% discounting rule was applied.

The ratio of the difference in total costs to the difference in change in QALYs, referred to as the incremental cost-effectiveness ratio (ICER)¹⁶, was the primary outcome. A bootstrap procedure was used to model the uncertainty in the ICER. A total of 5000 replicates were generated for which the estimates of the differences in cost and QALYs were computed. To characterize the uncertainty of the cost and effectiveness outcomes combined, the pairwise differences between costs and QALYs were plotted for the original data and the bootstrap estimates¹⁷. In addition, the bootstrap estimates of the cost-effectiveness acceptability curve, which plots the probability of having a positive net benefit for different monetary value thresholds per QALY, were generated and the standard thresholds of \$50,000 and \$100,000 were noted.

Sensitivity Analyses

Given the uncertainty surrounding current and future medication costs, sensitivity analyses were performed using a variety of cost assumptions as recommended by the Panel on Cost-

Effectiveness in Health and Medicine¹⁶. For medications other than the implant, analyses were performed applying prices equivalent to 10% to 40% reductions in the average wholesale price in 10% intervals. Additional sensitivity analyses were performed to determine the impact of specific high-cost immunosuppressant medications (cyclosporine and mycophenolate mofetil) that had highly variable reported costs in the literature. For the scenarios in which the implant was not cost-effective, the reductions in the cost of the implant necessary for the ICER to fall below the standard thresholds of \$50,000/QALY and \$100,000/QALY were calculated.

Results

The difference in change in QALYs between the two treatments favored the implant by a small margin; however, the difference was not statistically significant for either type of uveitis, bilateral (Difference Implant – Systemic [I-S] = 0.057, $p = 0.22$) or unilateral (I-S = 0.130, $p = 0.12$). In the case of bilateral disease, there was little or no change in QALYs (0.002, 95% CI: -0.064 to 0.068) during follow-up for the implant group whereas the systemic group had a slight, albeit not statistically significant, decline (-0.054, 95% CI: -0.118, 0.009) (Table 1, available at www.aaojournal.org). In contrast, both the implant (0.158, 95% CI: 0.033, 0.283) and systemic (0.028, 95% CI: -0.076, 0.133) groups had an improvement in QALYs for patients with unilateral disease, although it was only statistically significant for the implant group and the overall difference between the two groups was not statistically significant.

As expected, implant therapy had a large upfront cost with lower maintenance costs whereas systemic therapy costs were steady throughout the course of follow-up (Table 2, available at www.aaojournal.org). For the individuals with bilateral disease, the three-year cumulative cost (in US Dollars) was approximately \$69,300 in the implant group and \$52,500 in the systemic therapy group, a significant mean difference in average expenditure of \$16,900 (95% CI: \$7,400 to \$26,300, $p < 0.001$). For individuals with unilateral disease, the mean costs through three years was approximately \$38,800 in the implant group and \$33,400 in the systemic group; the mean greater expenditure of \$5,300 (95% CI: -\$8,400 to \$19,000) in the implant group was not statistically significant ($p = 0.44$).

In addition to total cost, we computed the fraction of cost due to different procedures and medications for each treatment both for each year of follow-up and overall (Figures 1a and 1b for bilateral and unilateral disease, respectively). Not surprisingly, more costs were incurred for medications (not including implants) in the systemic group and more costs were incurred for ophthalmologic procedures in the implant group. The only category that was approximately equal between groups was hospitalization. The additional medical costs in the systemic treatment arm were driven by the use of biologic and conventional immunosuppressive therapies. The excess procedure costs in the implant group were driven by cataract and glaucoma procedures.

For bilateral uveitis, the ICER through three years was \$297,800/QALY. The distribution of the paired differences in costs and QALYs from the 5000 bootstrap estimates was uniformly clustered around the point estimate with all but one of the differences in cost estimates

above 0, indicating that implant therapy was more expensive than systemic therapy (Figure 2a). Approximately 12% of the simulations were consistent with the implant not producing improved QALYs. Indeed, the probability of the ICER being cost-effective for bilateral disease was only 0.003 for a threshold of \$50,000/QALY and was 0.04 for a threshold of \$100,000/QALY, respectively (Figure 3). The price of the implant would need to be reduced to \$12,600 and \$14,500 to achieve ICERs below the \$50,000/QALY and \$100,000/QALY thresholds, respectively (Table 3). Discounting the medication prices overall or for specific immunosuppression medications that were costly and frequently used increased the ICER (further reducing the cost-effectiveness of implant therapy relative to systemic therapy).

In contrast, the ICER for unilateral disease was \$41,200/QALY at 3 years. The distribution of the bootstrap results was more variable in the univariate case than in the bivariate case (Figure 2b), reflecting the relatively fewer cases with unilateral uveitis ($N = 31$) enrolled in the trial. While the majority of bootstrap replicates were in the quadrant representing higher cost and more QALYs with implant therapy, the fraction that were in either the quadrant representing implant superiority (lower costs and higher QALYs, 20%) or the quadrant representing higher costs and lower QALYs with implant therapy (6%) was not negligible. The probability of the ICER being cost-effective was 0.53 for a threshold of \$50,000/QALY and was 0.74 for a threshold of 100,000/QALY, respectively (Figure 3). In sensitivity analyses that included medication discounts, the ICER increased beyond the \$50,000/QALY threshold but remained below \$100,000/QALY (Table 3). Reducing the price of the implant by 42% and 34%, the amounts required to be cost-effective for bilateral disease, results in implant superiority in terms of both lower cost ($I-C = -\$3,500$ and $-\$1,700$, respectively) and higher QALYs. Hence, the implant dominated in these scenarios.

Discussion

Our incremental cost-effectiveness analysis comparing implant to systemic therapy for intermediate, posterior, and panuveitis suggests that for bilateral uveitis cases, which made up 88% of the MUST Trial cohort, implant therapy incurs a higher cost than systemic therapy (\$69,300 versus \$52,500) to obtain a modest gain in QALYs ($D I-S = 0.057$), a gain which itself was not statistically significant ($p = 0.22$). The incremental cost-effectiveness ratio for implant vs. systemic therapy in bilateral uveitis was nearly \$300,000/QALY, which is considerably higher than the commonly used, if arbitrary, thresholds of \$50,000/QALY and \$100,000/QALY. In fact the implant would not be cost-effective at these thresholds unless the price were reduced by 42% and 34%, respectively. Given that implant therapy was considerably more successful in controlling inflammation than systemic therapy⁷, but that systemic therapy still succeeded in most cases, a more cost-effective strategy for individuals with bilateral disease may be to restrict implant therapy to cases which fail to be controlled with systemic therapy, require very expensive systemic therapies to gain control of inflammation, or when systemic therapies are contraindicated.

In contrast, the incremental cost-effectiveness ratio was reasonably favorable for implant therapy for individuals with unilateral uveitis, falling within the range generally considered cost-effective. However, the limited number of unilateral cases in the MUST Trial ($N = 31$) made the uncertainty associated with the estimates of the ICER higher for this subgroup

(Tables 1 and 2, Figure 2b). Hence, from a health economic perspective, implant treatment may be a reasonable approach for unilateral intermediate, posterior or panuveitis; nonetheless, additional study is needed as the inference for individuals with unilateral disease is limited due to the small sample size.

Relatively few incremental cost-effectiveness studies focusing on eye care have taken into account the impact of unilateral versus bilateral disease. However, there are several important issues to consider for this comparison. First, the price of the surgical approach will be nearly double for bilateral cases whereas the price of the systemic approach varies less substantially depending on laterality, which may lead to substantial differences for high cost local therapy approaches, such as fluocinolone acetonide implant therapy. Second, the quality of life impact is empirically higher (for both treatment groups) in the unilateral group compared with the bilateral group, perhaps due to the lesser burden of disease and treatment for a single eye. Third, a surgical procedure that is performed on both eyes puts vision at risk in a way that would not be the case with a unilateral approach. Each of these issues should be given further consideration when performing future cost-effectiveness studies related to eye care. A failure to consider the laterality at the population level may lead to the decision not to recommend a procedure for some groups when it is warranted (or vice-versa). Our results suggest that clinical guidelines derived from health economic analysis may vary by laterality in policy-relevant ways in conditions affecting paired or multiple organs.

The high utilization of immunosuppressive agents and other medications for which the reported prices were quite variable makes the estimate of ICER sensitive to assumptions about medication costs. However, our sensitivity analyses evaluating scenarios where these medications were less expensive did not qualitatively alter the conclusions made from the primary ICER analysis. With lower prices, the cost-effectiveness of implant therapy for bilateral disease became more unfavorable. The cost-effectiveness of implant therapy for unilateral uveitis also became less favorable, but remained more favorable than the \$100,000/QALY threshold (Table 3).

The MUST Trial was designed to compare the effectiveness of implant versus systemic therapy over two years⁷. However, the effect of the implant has been shown to last for three or more years³. Hence, an evaluation of three year data was required to provide an appropriate comparison of cost-effectiveness. Evaluation of the additional follow-up data provides insight into the incremental cost-effectiveness of the implant relative to systemic treatment. Regardless of laterality, the cost of therapy was significantly higher for individuals assigned to implant therapy as compared to those assigned to systemic therapy during the first year of follow-up (Table 2). This pattern was reversed for years 2 and 3 with systemic therapy being the more costly of the two treatments; thereby reducing the difference in cumulative cost of implant versus systemic therapy. Similarly, the relative gains for the improvement in health utility continued to accrue each year for the implant group, driven by stable (but small and not statistically significant) superiority in the EQ-5D scores in the implant group (Table 1). If the trends continue for a fourth year and beyond (i.e., should implants prove to last longer than three years on average) the overall difference in cost would continue to decrease while the relative utility would increase. Conversely, if re-implantation were required after the third year, then the cost of the implant would again

dominate the comparison between the two treatment options. Thus, a fuller understanding of the life expectancy of the implant is needed to better characterize the cost-effectiveness of the alternative treatment approaches. Continued follow-up of the MUST Trial cohort will provide valuable information to answer this question.

The main limitation for this study, other than the relatively small number of unilateral cases, was the inability to gather the cost data directly, either from a hospital cost accounting system or from billing and claims records. The use of Medicare reimbursement rates and other standard prices is an accepted alternative to direct measurement of cost data in the cost-effectiveness literature. The fact that the data on the dose and frequency of pharmaceutical products relied on average rather than actual doses is another limitation of the study. However, these two approaches may make the cost more generalizable from a payer's perspective because they mitigate the effects of idiosyncrasies in institutional billing and physician's prescribing patterns. Sensitivity analyses were conducted to assess the impact of different pricing schemes. In all cases, the inference remained stable although the point estimates of the ICER varied.

One of the goals of the MUST Trial was to compare the aggregate cost-effectiveness for implant versus systemic therapy. Given the observed results, a natural question is whether there are subgroups of patients with bilateral disease for which implant therapy would be cost-effective. The identification of such subgroups, if any exist, has the potential to play an important role in guiding clinical recommendations. This question is beyond the scope of the current manuscript and may in fact require additional sources of information beyond the MUST Trial given the limited sample size. Nonetheless, it would be an important direction for future research.

Moving forward, there likely will be many more opportunities to contrast medical and surgical methods of managing diseases. This analysis emphasizes the importance of considering the full length of time that a surgically implanted device is useful and, in the case of an eye disease, whether one or both eyes may be affected. The policy recommendations will vary among clinical situations depending on the complexity of the surgery, the cost of any device that is part of the procedure, and the cost of the pharmaceuticals used to manage the condition. Pricing changes for devices or procedures also may have a large impact on costs, which could change the qualitative interpretation of health economic analyses of this nature, as demonstrated by the ability of the implant to be considered cost-effective for bilateral disease if the price were reduced by 34%–42%. Therefore, any policy recommendations based on such analyses may need to be reconsidered should pricing changes occur.

In summary, for this incremental cost-effectiveness analysis of alternative treatment regimens for intermediate, posterior, and panuveitis, the fluocinolone acetonide implant was found to be an economically favorable option for individuals with unilateral uveitis but not an economically favorable option for those with bilateral disease. However, our conclusions do not apply to the scenario of using implant therapy in eyes where systemic therapy has failed or is contraindicated. Empirical determination of the duration of implant effect or large changes in pricing may necessitate a re-evaluation of this cost-effectiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Percentage of total cost attributable to implant, procedure, uveitis medication, ocular medication, other medication, and hospitalization over three years of follow-up for individuals randomized to systemic (left) or implant (right) therapy for individuals with bilateral (a) and unilateral (b) disease.

Figure 2.

Bootstrap estimates of the variability of the components of the incremental cost effectiveness ratio comparing implant and systemic therapy for individuals with (a) bilateral uveitis and (b) unilateral uveitis. The black dot represents the pairing of the estimated difference in cost and quality adjust life years (QALYs) based upon the observed data. The grey x's represent the bootstrap replicates. The upper left (systemic) and lower right (implant) quadrants represent scenarios for which one therapy is dominant.

Figure 3.

A plot of the probability that implant therapy is cost-effective versus the threshold of dollars per quality adjusted life year (QALY) used to define cost-effectiveness for bilateral (black) and unilateral (grey) disease. The probability of being cost-effective is included for the standard thresholds, \$50,000/QALY (triangle) and \$100,000/QALY (square).

Table 3

Sensitivity of the incremental cost-effectiveness ratio (ICER) to treatment pricing for individuals with bilateral and unilateral uveitis. The ICERs are computed using the estimated differences in quality adjusted life years (QALYs) for unilateral (0.057) and bilateral (0.130) disease.

Medication pricing	Difference in Cost*	ICER* [†] (\$/QALY)
Bilateral Uveitis		
Original estimates	\$16,900	\$297,800/QALY
Medication discount (excluding implant)		
Overall		
10%	\$19,200	\$339,200/QALY
20%	\$21,500	\$380,600/QALY
30%	\$23,900	\$421,900/QALY
40%	\$26,200	\$463,300/QALY
Immunosuppression agents (50% discount)		
Cyclosporine	\$17,900	\$317,100/QALY
Mycophenolate mofetil	\$21,500	\$379,600/QALY
Reduced implant price (% reduction)		
\$12,600 (42%)	\$2,800	\$48,800/QALY
\$14,500 (34%)	\$5,600	\$99,700/QALY
Unilateral Uveitis		
Original estimates	\$5,300	\$41,200/QALY
Medication discount (excluding implant)		
Overall		
10%	\$7,000	\$54,300/QALY
20%	\$8,700	\$67,400/QALY
30%	\$10,400	\$80,500/QALY
40%	\$12,100	\$93,600/QALY
Immunosuppression agents (50% discount)		
Cyclosporine	\$6,800	\$52,100/QALY
Mycophenolate mofetil	\$9,800	\$75,800/QALY
Reduced implant price (% reduction)		
\$12,600 (42%)	−\$3,500	n/a
\$14,500 (34%)	−\$1,700	n/a

* All estimates are rounded to the nearest 100 dollars

[†] A value of 'n/a' is used to indicate situations in which implant therapy dominates systemic therapy in terms of both cost and QALYs.