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A Bayesian Analysis of a Randomized Clinical Trial Comparing Antimetabolite Therapies for Non-Infectious Uveitis

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Abstract

Purpose—To conduct a Bayesian analysis of a randomized clinical trial (RCT) for non-infectious uveitis using expert opinion as a subjective prior belief.

Methods—A RCT was conducted to determine which antimetabolite, methotrexate or mycophenolate mofetil, is more effective as an initial corticosteroid-sparing agent for the treatment of intermediate, posterior, and pan- uveitis. Before the release of trial results, expert opinion on the relative effectiveness of these two medications was collected via online survey. Members of the American Uveitis Society executive committee were invited to provide an estimate for the relative decrease in efficacy with a 95% credible interval (CrI). A prior probability distribution was created from experts' estimates. A Bayesian analysis was performed using the constructed expert prior probability distribution and the trial's primary outcome.

Results—11 of 12 invited uveitis specialists provided estimates. Eight of 11 experts (73%) believed mycophenolate mofetil is more effective. The group prior belief was that the odds of treatment success for patients taking mycophenolate mofetil were 1.4-fold the odds of those taking methotrexate (95% CrI 0.03 – 45.0). The odds of treatment success with mycophenolate mofetil compared to methotrexate was 0.4 from the RCT (95% confidence interval 0.1–1.2) and 0.7 (95% CrI 0.2–1.7) from the Bayesian analysis.

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Conclusions—A Bayesian analysis combining expert belief with the trial's result did not indicate preference for one drug. However, the wide credible interval leaves open the possibility of a substantial treatment effect. This suggests clinical equipoise necessary to allow a larger, more definitive RCT.

INTRODUCTION

Traditionally, clinical trials are designed and analyzed from a frequentist perspective using classical hypothesis testing. However, there is a growing awareness of the usefulness of Bayesian methods which, using Bayes' theorem, can incorporate previous knowledge on the likelihood of an event into the interpretation of trial results.[1–7] To conduct a Bayesian analysis first requires quantifying existing information or belief prior to the release of the trial's outcome.[6] One way to do this is by surveying experts. Before a trial is conducted, clinicians may have opinions on the relative effectiveness of treatments, formed through clinical experience or from knowledge of previous studies. These beliefs can be combined and expressed as a probability distribution.[8]

Uveitis is a group of conditions defined by intraocular inflammation and although uncommon, accounts for up to 10% of legal blindness in the United States.[9] Uveitis is classified by etiology (infectious or non-infectious) and by anatomical location (anterior, intermediate, posterior, and/or pan-uveitis). Corticosteroids are the conventional first-line treatment for non-infectious uveitis. However, in some patients who have chronic uveitis, corticosteroid-sparing therapy is often started because of the significant side effects of long-term steroid use. Methotrexate and mycophenolate mofetil are two antimetabolites commonly used as corticosteroid-sparing agents in the treatment of chronic uveitis.[10] Several retrospective studies have shown these treatments to be effective in controlling ocular inflammation[11–15] but there is a lack of comparative, prospective studies. Our group recently conducted a randomized clinical trial (RCT) to determine which antimetabolite, methotrexate or mycophenolate mofetil, is more effective as an initial corticosteroid-sparing agent in controlling ocular inflammation.[16]

In this paper we report the results of a Bayesian analysis of a RCT for non-infectious intermediate, posterior, and pan-uveitis to assess how prior expert opinion influences the interpretation of the trial results. We describe the methods for eliciting and constructing a prior probability distribution based on expert opinion and compare the Bayesian result to that of the frequentist approach.

MATERIALS AND METHODS

Trial synopsis

A RCT was conducted to compare the proportion of patients achieving corticosteroid-sparing control of inflammation with methotrexate versus mycophenolate mofetil. Treatment success (corticosteroid-sparing control of inflammation) was defined by achieving the following at the 5-and 6-month study visit: 1) ≤0.5+ anterior chamber cells, ≤0.5+ vitreous cells, ≤0.5+ vitreous haze, and no active retinal/choroidal lesions; 2) ≤10mg of oral

prednisone daily and ≤2 drops of prednisolone acetate 1% (or equivalent) a day; and 3) no declaration of treatment failure from intolerability or safety.

The details of the trial have been described previously.[16] Briefly, patients ≥16 years of age with intermediate, posterior, or pan-uveitis requiring corticosteroid-sparing therapy were enrolled between October 2011 and June 2012 at Aravind Eye Hospitals in Madurai and Coimbatore, South India. All were randomized to receive 25mg/week oral methotrexate or 2g/day mycophenolate mofetil, and were monitored monthly for 6 months. Corticosteroids were tapered. A total of 80 patients were block-randomized in a 1:1 ratio within clinic (permuted blocks of size 4 and 6) to have 80% power to detect a 30% difference in treatment success. Ophthalmologists and visual acuity examiners were masked. Institutional review board approval was obtained from the University of California, San Francisco and Aravind Eye Hospitals. The trial was compliant with the Health Insurance Portability and Accountability Act of 1996, adhered to the Declaration of Helsinki, and all patients provided written informed consent.

Construction of prior probability distribution from expert opinion

A clinician's belief can be expressed as a probability and converted into a probability distribution. For a Bayesian analysis, a prior probability distribution is created to summarize clinicians' beliefs about the efficacy of a treatment.[3,5] The prior distribution was created by surveying expert opinion on methotrexate and mycophenolate mofetil for the treatment of noninfectious intermediate, posterior, and pan-uveitis before the release of the trial results. An online survey invitation was emailed in September 2012 to the American Uveitis Society executive committee, which is made up of 12 uveitis specialists in the US. The online survey (Appendix) outlined the objective of the study and invited experts to share their prediction of the trial's results. The US committee was chosen because of the members' experience managing patients with mycophenolate mofetil and methotrexate, in contrast to other places such as India where the expense of mycophenolate mofetil limits its use relative to methotrexate.

The survey provided background information on the trial including sample size, anatomical types of uveitis, follow-up time, treatment dosing, and the definition of corticosteroid-sparing control of inflammation (or treatment success). Experts were first asked to choose which drug, methotrexate or mycophenolate mofetil, is better for controlling intermediate, posterior, and pan-uveitis. They were then asked to select if they believed one drug was 0%, 25%, 50%, 75%, or 100% less effective relative to the other with an upper and lower limit for their belief, ie, a 95% credible interval (CrI). All results were collected using SurveyMonkey (SurveyMonkey.com, accessed September 2012).

A discretized prior distribution was created for each expert by finding the distribution that would minimize the Fisher information, given the desired mean relative decrease and 95% CrI provided by each respondent .[17] Note that if an expert's bounds were symmetric around his/her estimate, the prior would then approach a normal distribution, but asymmetric bounds would produce a skewed distribution. The individual priors were then summed and normalized to create the overall expert subjective prior distribution. The normalized group

prior was transformed from a relative percent decrease in effectiveness to a log-odds scale. A similar method has been used previously.[8,18–21]

Bayesian analysis

The posterior distribution was created using Bayes' theorem. The likelihood function from the result of the trial was multiplied by the prior distribution and normalized to create the posterior distribution. Prior and posterior distribution calculations were performed using Mathematica (Mathematica 8, Wolfram Research, Champaign, IL, USA). Descriptive statistics and graphics were created using R (The R Project for Statistical Computing, version 3.0.2, Vienna, Austria, available at: http://www.r-project.org).

RESULTS

Survey results

All 12 invited uveitis specialists responded to the survey. Table 1 describes the characteristics of the participating experts. 10 (83%) had been practicing between 5 and 10 years and mainly in a university or academic setting (n=11, 92%). 10 of 12 specialists (83%) "always" or "almost always" prescribe or manage/directly implement methotrexate and mycophenolate mofetil therapy themselves. All confirmed they had no prior knowledge of the trial results. All but one (92%) provided input on which treatment s/he felt was more efficacious, and 10 of 12 (83%) provided estimates for the relative difference in treatment success for the drugs.

Overall, 8 of 11 experts (73%) thought mycophenolate mofetil is better for controlling ocular inflammation. Each specialist's belief with a 95% CrI is depicted in Figure 1. Five of the 10 experts (50%) believed methotrexate would be ≥25% less effective than mycophenolate mofetil. Four (40%) estimated the trial would see no difference between the two drugs. Only one expert (10%) thought that methotrexate would be more effective.

Group prior belief

The blue curve in Figure 2[ED:ensure colour image production in print] depicts the group prior distribution transformed into the log-odds scale. The probability that mycophenolate mofetil is more effective than methotrexate is the area under the curve to the right of the dashed line. The area to the right of 1 is 0.70, implying the community of experts felt there was a 70% chance mycophenolate mofetil was better than methotrexate. The odds of treatment success for those taking mycophenolate mofetil was estimated to be 1.4-fold the odds of those taking methotrexate (mean odds ratio 1.4, 95% CrI 0.03–45.0).

Trial results

Of the 80 patients enrolled, 67 contributed to the primary analysis. 15 of 32 patients (47%) taking mycophenolate mofetil achieved corticosteroid-sparing control of inflammation compared with 24 of 35 (69%) taking methotrexate (mean odds ratio mycophenolate mofetil to methotrexate 0.4, 95% confidence interval, CI, 0.1–1.2, P=0.09). A frequentist analysis of the trial has been previously reported.[16] The likelihood function of the trial result is depicted by the red curve in Figure 2.

Bayesian analysis

We generated a posterior distribution using the group expert prior and the primary outcome from the trial (Figure 2). The posterior distribution has a peak at an odds ratio of 1. The mean odds ratio was 0.7 (95% CrI 0.2–1.7), meaning the odds of treatment success for a patient taking mycophenolate mofetil was 0.7 times the odds of a patient taking methotrexate. The area to the right of 1 is 0.28. Therefore, the posterior probability suggests there is a 72% chance that methotrexate is superior to mycophenolate mofetil, a 46% chance that methotrexate has at least 1.5-fold odds of success compared with mycophenolate mofetil, and a 30% chance of at least a 2-fold odds of success compared with mycophenolate mofetil.

DISCUSSION

A RCT was conducted to address which antimetabolite, methotrexate or mycophenolate mofetil, is more effective in controlling ocular inflammation in patients with non-infectious intermediate, posterior, or pan-uveitis. Before the release of trial results, expert opinion on the comparative effectiveness of these two medications was collected and used for a secondary Bayesian analysis. We combined the prior expert opinion with results from our trial to create a posterior probability distribution using Bayes' theorem.

In general, experts believed mycophenolate mofetil is more effective at controlling inflammation. This is in line with results from a previous survey where uveitis specialists preferred mycophenolate mofetil over other immunosuppressive agents as an initial corticosteroid-sparing treatment for intermediate, posterior, and pan-uveitis.[22] This opinion may have formed through clinical experience or knowledge of previously reported success rates. A retrospective cohort study published in 2008 comparing antimetabolite efficacy in intermediate, posterior, and pan-uveitis patients suggested corticosteroid-sparing success was achieved by 6 months in 79% of patients on mycophenolate mofetil and 42% on methotrexate.[11] Overall, non-comparative retrospective case series have reported success rates ranging from 37–76% for methotrexate[11–13,23] and 54–96% for mycophenolate mofetil.[11,14,15,24,25] It is difficult to know which drug is more efficacious from these studies because of varying definitions of controlled inflammation and inherent study biases such as treatment-by-indication bias, differences in dosing and differing follow-up times. Although most uveitis specialists in this survey favored mycophenolate mofetil, half of those favoring mycophenolate mofetil provided wide enough CrIs that allowed for the possibility of methotrexate to be more effective. The prior distribution, which is a summary of all specialists' opinions, leans toward mycophenolate mofetil being more effective, and the wide tails of the distribution reflect the lack of certainty in this opinion.

The frequentist analysis found the odds of treatment success for patients taking methotrexate were nearly two and half times the odds for those taking mycophenolate mofetil, although this was not statistically significant (P=0.09). The posterior distribution was created by updating the prior with the trial's likelihood distribution. The posterior's mean odds ratio was near one, suggesting there is insufficient evidence to prefer one medication over the other, given the available prior belief. However, the wide CrI leaves open the possibility of a treatment effect; based on the posterior distribution, there is nearly 50% chance that the odds

of treatment success with methotrexate are ≥1.5-fold the odds of success with mycophenolate mofetil.

Bayesian analysis of trial data has several differences from frequentist analysis. First, Bayesian methods incorporate the realm of current knowledge or belief into the analysis. This is done through the creation of a prior distribution which reflects a summary of what is known from previous studies or clinical experience. Creating a distribution outlines the landscape of current knowledge, providing information on the level of certainty of current opinion.[3,8] Although in general mycophenolate mofetil was thought to be more effective, there was not much confidence around this belief as indicated by the relatively heavy tails of the prior distribution. Second, Bayesian analysis conclusions are not dichotomized (as significant or not) or limited by P-value interpretations but rather allowed to be seen as a continuum. It is well known that insufficient power accompanying small trials may lead to insignificant P-values even when clinically meaningful effects are observed.[2,4] If the results of a trial contradict the beliefs of practicing clinicians, it may be difficult to convince them otherwise with frequentist methods alone. Bayesian methods more closely reflect the natural thought process, and the posterior distribution visually represents how previous beliefs should change after the release of trial results.

However, the implementation of Bayesian methods requires the specification of a prior distribution, which is often the subjective assessment of an expert. A possible limitation of this analysis was in the questioning used to elicit the prior. Elicitation was based on CrIs, a statistical concept possibly less intuitive to the experts, and the survey had a fixed set of estimate options (in 25% increments). An alternative approach may have produced a different subjective prior distribution. Another limitation was performing the analysis with only a single prior distribution; using a different group of experts or a non-informative prior distribution may have given a different posterior distribution. The survey was limited to a small group of content experts, which may not make it generalizable to all ophthalmologists. Although the sample of experts was small, the response rate was high; we had 11 of 12 experts participate. Of note, the wide tails of the prior distribution are not the result of surveying a small number of experts but rather a reflection of the experts' uncertainty in which drug is better. Furthermore, uveitis is a heterogeneous group of conditions and a limitation of the survey and the trial is that all types of uveitis were analyzed together. Clinicians might have had different opinions about the medications if asked about a specific type of uveitis.

In conclusion, the survey showed that experts believed mycophenolate mofetil 2g/day is more effective than methotrexate 25mg/week. A small randomized clinical trial, whose results were revealed only after the survey was conducted, estimated the mean odds of treatment success with mycophenolate mofetil was 0.4-fold the odds of success with methotrexate (95% CI 0.1–1.2). A Bayesian analysis combining the survey belief and the results of the trial did not prefer one drug and allowed for the possibility of a range of effect sizes favoring either drug. Neither the expert survey nor the frequentist analysis of the RCT offered particularly compelling evidence for equipoise. However, combining the two in a Bayesian analysis suggests there is clinical equipoise necessary to allow a larger, more definitive RCT.

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APPENDIX: Survey Questions

We are interested in your perceptions of the efficacy of methotrexate versus mycophenolate mofetil. We recently completed a pilot clinical trial comparing these two medications as corticosteroid-sparing therapy for uveitis. We consider you an expert in this field and would appreciate your prediction of our results. We are planning to conduct a Bayesian analysis of the trial, and your prediction of the outcome will be taken into account for the analysis.

Thank you for taking time to participate in this survey. It should take approximately 5 minutes and your results will be anonymous.

A pilot trial compared the efficacy of methotrexate and mycophenolate mofetil in treating non-infectious intermediate, posterior, and pan uveitis. Eighty patients in need of corticosteroid-sparing therapy were randomized to receive either oral methotrexate (at a maintenance dose of 25 mg a week) or oral mycophenolate mofetil (at a maintenance dose of 1 gram twice a day), in addition to receiving oral corticosteroid therapy. They were followed monthly for 6 months after enrollment or until treatment failure. The primary aim of this pilot was to determine which therapy (methotrexate or mycophenolate mofetil) was more effective in achieving corticosteroid-sparing control of inflammation defined by:

Inflammation Markers:

- ≤.5+ Anterior Chamber Cells
- ≤.5+ Vitreous Cells
- ≤.5+ Vitreous Haze
- No active choroidal and retinal lesions

Corticosteroid Levels:

- Prednisone dose ≤ 10 mg/day
- Topical corticosteroids ≤ 2 drops/day

Patients were considered a success if they met the above criterion, in both eyes, at their Month 5 and 6 assessments.

When answering the following questions please consider all of the information you have available to you including experience in clinical practice, knowledge of literature, and discussions with colleagues. Although you do not have to answer each question, we would appreciate if you do so.

*1 Are you aware of the results of this pilot trial? Results have not yet been publically presented or published, so any knowledge would have had to come through one of the investigators.

☐ Yes ☐ No

2 How many years have you been practicing as a uveitis specialist? (please select one)

☐ > 0 and < 5 ☐ ≥ 5 and <10 ☐ ≥ 10 and above

3 Do you manage therapy with methotrexate yourself?

☐ Never ☐ Almost Never ☐ Sometimes ☐ Almost Always ☐ Always

4 What is the most common dose you use for oral methotrexate? (type “N/A” if this does not apply to you)

Intial dose (mg/wk) _____

Maintenance dose (mg/wk) _____

5 Do you manage therapy with mycophenolate mofetil yourself?

☐ Never ☐ Almost Never ☐ Sometimes ☐ Almost Always ☐ Always

6 What is the most common dose you use for oral mycophenolate mofetil? (type “N/A” if this does not apply to you)

Intial dose (mg/wk) _____

Maintenance dose (mg/wk) _____

7 How would you characterize the setting of your practice?

☐ Private/Solo ☐ Private Group Practice ☐ University/Academic ☐ HMO

8 Where is your practice located?

☐ Africa ☐ Asia ☐ Australia ☐ Canada ☐ Europe ☐ Latin America ☐ United States

9 Which of the following do you think is better at achieving corticosteroid-sparing control?

☐ Mycophenolate Mofetil (MMF) ☐ Methotrexate (MTX)

10 Please provide your best estimate for the relative decrease in efficacy between the two drugs (in terms of a percentage) and describe the certainty you have about this estimate.

In the BEST ESTIMATE row, please specify how much worse you expect [DRUG NOT CHOSEN IN PREVIOUS QUESTION] to perform, compared to [DRUG CHOSEN IN PREVIOUS QUESTION]

Please specify and UPPER and LOWER LIMIT between which you believe the estimate is almost certain to lie. Think of this as a 95% confidence interval. Your interval need not be symmetric.

	MMF 100% less effective	75%	50%	25%	0 (no difference)	25%	50%	75%	MTX 100% less effective
Best Estimate	☐	☐	☐	☐	☐	☐	☐	☐	☐
Upper Limit	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lower Limit	☐	☐	☐	☐	☐	☐	☐	☐	☐

Note that 0 indicates no difference between treatment arms, the options to the left of 0 indicate that mycophenolate mofetil performs worse, and the options to the right of 0 indicate that methotrexate performs worse. MMF = Mycophenolate Mofetil, MTX = Methotrexate

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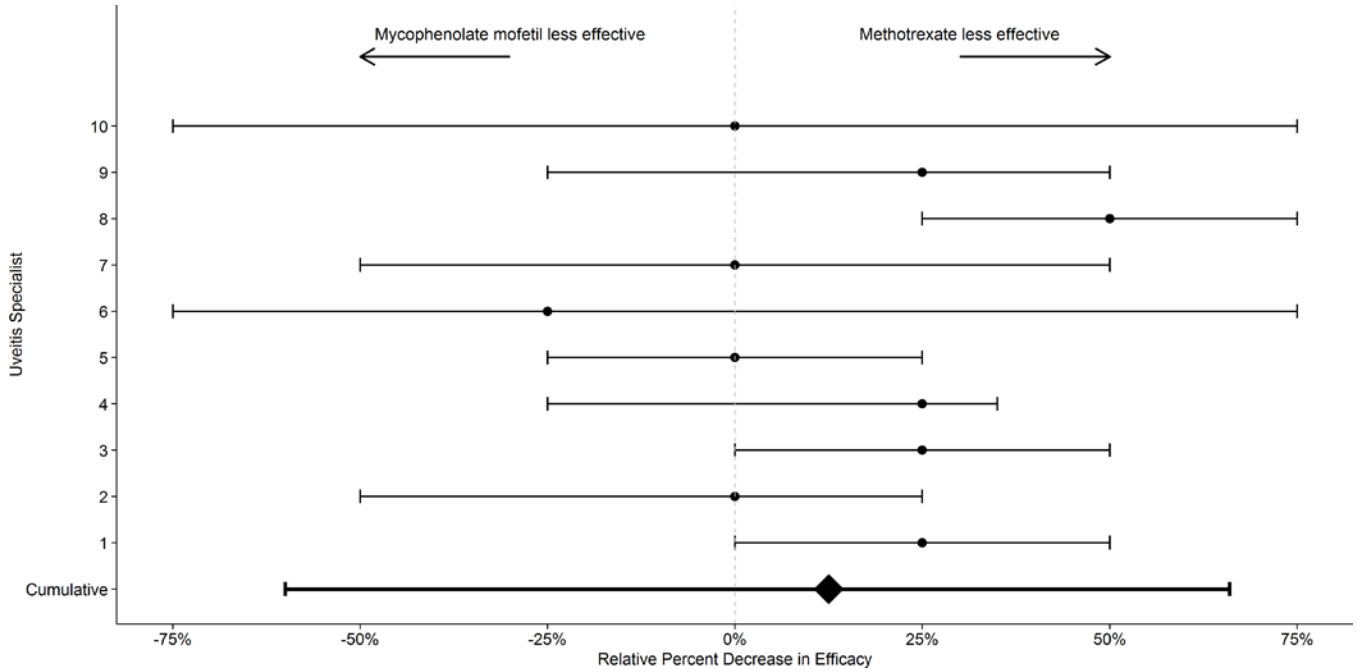

Figure 1.

Uveitis specialists were surveyed on which drug, methotrexate or mycophenolate mofetil, is better for treatment of noninfectious intermediate, posterior, or pan-uveitis and were asked to provide an estimate of the relative decrease in effectiveness of one drug compared to the other with a 95% credible interval. The figure displays the point estimate with 95% credible interval provided by the 10 specialists and the cumulative group belief.

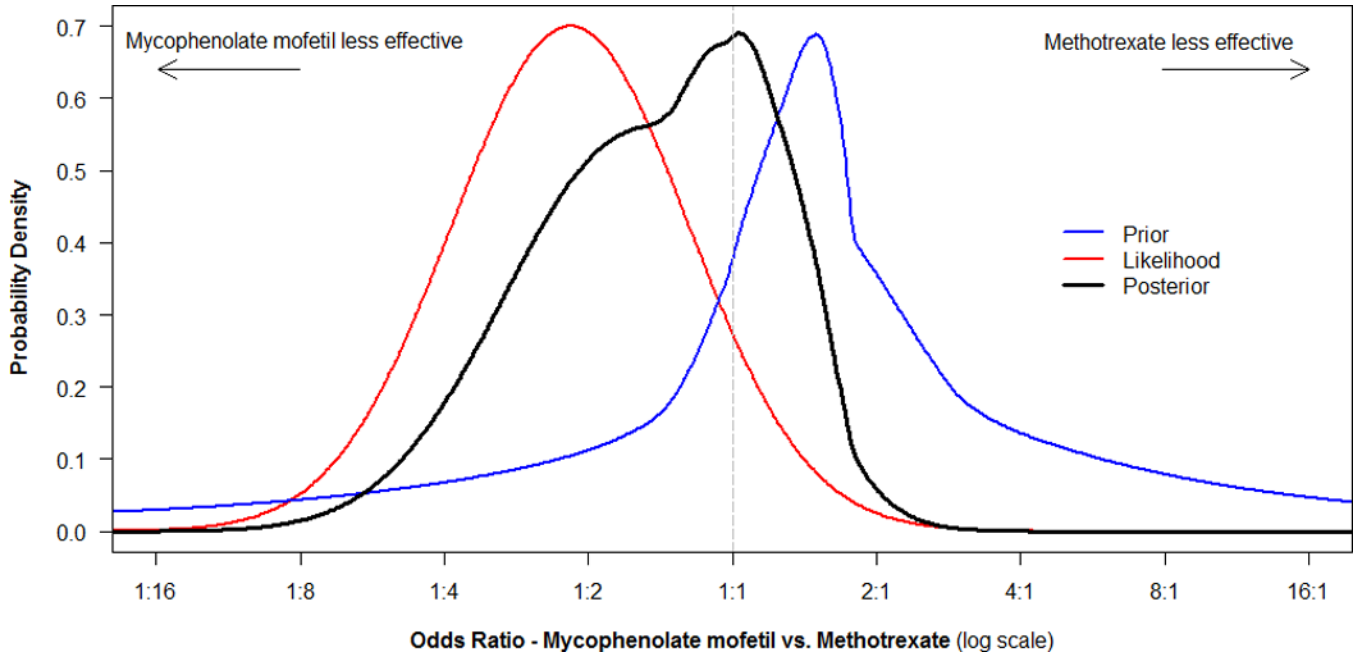

Figure 2.

Plots of the prior distribution (blue), the likelihood of the trial results (red), and the posterior distribution (black) from a Bayesian analysis of a randomized clinical trial comparing methotrexate to mycophenolate mofetil for treating noninfectious uveitis. The prior distribution was created by expert opinion collected through an online survey. The likelihood function was from the frequentist result of the trial. Curves are plotted on the log-odds ratio scale, and points along the x-axis are labeled with the corresponding odds ratio.

Table 1

Characteristics of 12 uveitis specialists surveyed to create a prior distribution for a Bayesian analysis of a clinical trial comparing methotrexate to mycophenolate mofetil for treatment of noninfectious uveitis.

Characteristic	**n**	**(%)**
	12	(100)
Years practicing		
<5	2	(17)
5–9	10	(83)
Setting of practice		
University/academic	11	(92)
Private group practice	1	(8)
Location of practice		
United States	12	(100)
Manage/directly implement methotrexate therapy		
Never	0	(0)
Sometimes	2	(17)
Almost always	3	(25)
Always	7	(58)
Manage/directly implement mycophenolate mofetil therapy		
Never	0	(0)
Sometimes	2	(17)
Almost always	3	(25)
Always	7	(58)