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An Adaptive Bayesian Design for Personalized Dosing in a Cancer Prevention Trial

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Abstract

Introduction—In biomarker-driven clinical trials, translational strategies typically involve moving findings from animal experiments to human trials. Typically, the translation is static, using a fixed model derived from animal experiments for the duration of the trial. But Bayesian designs, capable of incorporating information external to the experiment, provide a dynamic translational strategy. The current article demonstrates an example of such a dynamic Bayesian strategy in a clinical trial.

Methods—This study explored the effect of a personalized dose of fish oil for reducing prostaglandin E₂, an inflammatory marker linked to colorectal cancer. A Bayesian design was implemented for the dose-finding algorithm that adaptively updated a dose–response model derived from a previously completed the animal study during the clinical trial. In the initial stages of the trial, the dose–response model parameters were estimated from the rodent data. The model was updated following a Bayesian algorithm after data on every ten to 15 subjects were obtained until the model stabilized. Subjects were enrolled in the study between 2013 and 2015, and the data analysis was carried out in 2016.

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Results—Three dosing models were used for groups of 16, 15, and 15 subjects. The mean target dose significantly decreased from 6.63 g/day (Model 1) to 4.06 g/day (Model 3) ($p=0.001$). Compared with the static strategy of dosing with a single model, the dynamic modeling reduced the dose significantly by about 1.38 g/day, on average.

Conclusions—A Bayesian design was effective in adaptively revising the dosing algorithm, resulting in a lower pill burden.

Trial registration—This study is registered at www.clinicaltrials.gov [NCT01860352](https://clinicaltrials.gov/ct2/show/study?term=NCT01860352).

INTRODUCTION

Adaptive designs have been used with increasing frequency over several decades in clinical trials.^{1–3} They have multiple benefits over traditional RCTs. Adaptive designs allow the investigator to learn from and react to earlier findings from the trial, potentially reducing the sample size. They also provide the investigator the opportunity to search for the optimal treatment dose during the course of the trial, thereby enhancing the chance of finding true benefit.

Adaptive trials have been particularly useful for first-in-human Phase I dose–response studies with a small number of subjects.^{4–6} These trials assign doses based on cumulative toxicity data with the purpose of finding a safe dose for the patients. Traditional adaptive dose-finding strategies include 3 + 3 designs,⁷ and the Continual Reassessment Method,⁸ among others. Contemporary methods include Bayesian optimal interval designs⁹ and modified toxicity probability interval design.¹⁰ Adaptive designs also play a significant role in confirmatory trials. The fundamental strategy is a fixed and pre-specified plan for changes in the conduct of a trial carried out sequentially in a statistically valid fashion on the basis of evidence accumulated during the course of the trial.

Dose–response modeling using Bayesian adaptive strategies require, among other things, extensive probabilistic simulation of trial performance in the pursuit of the most efficacious treatment regions. A key feature of Bayesian adaptive designs is that interim analyses can be conducted frequently, allowing decision rules based on predictive probabilities conditioned on already observed data.

The application of a Bayesian design in translating the information from an animal experiment into the human clinical trial is, to the authors' knowledge, novel. The primary objective of the NIH-supported clinical trial “A Phase Ib Study of the Effects of Omega-3 Supplementation on Fatty Acid Metabolism on the Colon” ([NCT01860352](https://clinicaltrials.gov/ct2/show/study?term=NCT01860352)) conducted at the University of Michigan was to determine personalized doses of omega-3 fatty acid supplement that would result in a 50% reduction in colonic mucosal prostaglandin E₂ (PGE₂) compared to baseline. The role of PGE₂ in colon carcinogenesis has been well established in experimental studies. PGE₂ promotes carcinogenesis and invasive neoplastic progression by multiple mechanisms that include triggering Wnt signaling, increasing transcription of peroxisome proliferator-activated receptor- α via phosphoinositide 3-kinase/protein kinase B activation, and providing coordinated regulation of tumor immunosuppression.^{11–13} The preponderance of rodent data suggest that a reduction in

colonic neoplasia is associated with roughly a 50% reduction in colonic mucosal PGE₂.^{14–19} Data on the role of PGE₂ in colonic homeostasis suggest that a partial, but not complete, reduction in PGE₂ is optimal for achieving anti-inflammatory effects while maintaining gut barrier integrity.²⁰ The clinical trial was therefore designed to reduce colonic PGE₂ by 50%.

Previous clinical studies indicated that colonic PGE₂ in humans is highly variable.^{21–24} It was anticipated that characteristics such as age, sex, BMI, and dietary habits play major roles in the ability of omega-3 dietary supplement to reduce PGE₂, thereby necessitating personalized doses. A protocol was therefore established that would account for human biological variation by developing a new strategy to personalize dosing of omega-3 fatty acids for reducing colonic mucosal PGE₂.

The PGE₂ measures were obtained from colonic biopsies only twice, at baseline and the end of the trial, as colonoscopy and sigmoidoscopy are invasive procedures. Hence, an assessment of target dose based on the direct measurement of PGE₂ after providing varying doses was not possible. Omega-3 fatty acids can interfere with PGE₂ synthesis from arachidonic acid (AA) by limiting the available arachidonic acid to the metabolizing enzymes, cyclooxygenases-1 and 2 and by inhibiting cyclooxygenase 1.²⁵ In this regard, the ratio of eicosapentaenoic acid (EPA) to the arachidonic acid (EPA:AA) in serum acts as a surrogate marker for colonic PGE₂. In the clinical trial, EPA:AA was measured twice at baseline, and after both low and high doses of omega-3 fatty acids. The target omega-3 fatty acid dose was defined to be the smallest dose needed by a subject to increase their own serum EPA:AA ratio by an amount that would be predicted to decrease their colon PGE₂ by 50%.

A preliminary study in F-344 rats showed that serum EPA:AA had a strong log-linear relationship with PGE₂ in the colonic mucosa.²⁶ The Bayesian strategy was implemented to translate this information from the rodent trial into the human trial. The initial model was based on data from the rodent study. As more data from the human trial accrued, the model was updated in batches with (re)weighted information from the rodent study and the clinical trial. This paper serves as a statistical companion to the outcomes paper,²⁷ detailing the nuances of the Bayesian strategy and its potential use in future translational trials.

METHODS

Trial participants were aged 25–75 years, had BMI between 18 and 40 kg/mg², and were in good health without known colonic diseases. History of prior cancer diagnosed within last 5 years was an exclusion criterion, with the exception of surgically excised basal cell or squamous cell tumors of the skin. The trial was approved by the University of Michigan IRB. Participants were recruited between January 2013 and September 2015 locally through a University of Michigan web-based registry and advertisement at the medical center and community sites. Further details for recruitment and eligibility are provided in the outcomes paper.²⁷

Every subject was administered three doses of omega-3 fatty acid supplement: low, high, and the target dose projected to achieve a 50% reduction in colonic PGE₂ from baseline. The

supplement was provided in the form of 1 g capsules (EPA-Xtra, Nordic Naturals). At study entry, after undergoing a blood draw and a colonic biopsy to provide baseline values, every subject received a low dose of omega-3 fatty acids designed to approximate a dietary EPA:omega-6 fatty acid ratio of 0.1 for 2 weeks. A similar calculation was done for the high dose, utilizing a dietary EPA:omega-6 fatty acid ratio of 0.3. The values of 0.1 and 0.3 were consistent with the animal study, within which most of the changes in PGE₂ occurred.²⁶ The low and high doses were personalized for each subject based on their omega-6 fatty acid consumption, which was estimated from their expected caloric intake. The calculation uses the Harris-Benedict formula²⁸ utilizing a subject's age, sex, height, and weight (details provided in Appendix 1). After 2 weeks on each of the doses, a blood draw was done and serum EPA:AA was measured. The dose versus serum EPA:AA response using the baseline, low-, and high-dose data was almost perfectly linear for all subjects (minimum R² was 95%). Using the linearity between the dose and EPA:AA ratio, the personalized target dose (number of pills) was calculated as a function of the desired target EPA:AA as:

$$Dose_{target} = \frac{EPA:AA_{target} - A}{B},$$

where A and B are the intercept and slope estimates of the least squares linear fit through the individual data on dose and EPA:AA (baseline, low, and high dose). Thus, the only component required in calculating the target dose is the target EPA:AA, which was obtained using the steps described next.

The target EPA:AA for every subject was that measure that corresponds to a 50% reduction of his/her measured baseline PGE₂ (Figure 1, Panel A). The log-linear relationship between the two can be expressed by the equation:

$$E(\ln(PGE_2)) = \beta_1 + \beta_2 \times (EPA:AA) \quad (1),$$

where β_1, β_2 are the intercept and the slope of the line connecting natural logarithm of PGE₂ and EPA:AA, respectively. Based on Equation 1, a 50% reduction in PGE₂ compared with its baseline value translates to a target EPA:AA via the equation:

$$EPA:AA_{target} = EPA:AA_{baseline} + \left(\frac{\ln(0.5)}{\beta_2} \right) \quad (2).$$

The offset $\ln(0.5)/\beta_2$ in Equation 2 explicitly demonstrates the role of the mathematical expression depicting the colonic PGE₂ versus serum EPA:AA relationship.

In the initial stage of the trial, the estimate of β_2 in Equation 2 was obtained from the rodent data. The model was updated following a Bayesian algorithm after data on every ten to 15 subjects were obtained until the model stabilized (i.e., did not change appreciably). The algorithm that was pivotal in the adaptive process is described next.

Bayesian Biomarker Adaptation Algorithm

A Bayesian approach was used to model the relationship between PGE_2 and EPA:AA in Equation 1. The logarithm of PGE_2 was assumed to be a linear function of EPA:AA, which is determined by an intercept parameter and a slope parameter as specified in Equation 1. The main idea is summarized as follows: Before any human data were collected, the rodent data were used to estimate the model parameters. As the first cohort of human data became available, both the human data and the rodent data were used to re-estimate the model parameters. The updated parameter estimate was a weighted average of the estimate from the rodent data and the estimate from the human data, with the weight inversely proportional to the variance of the estimators. As more human data became available, greater weight was put on the human data when combining with the rodent data. Thus, the model parameters were estimated adaptively, leading to a personalized target dose based on the subject's dose versus EPA:AA relationship (Figure 1, Panel B). This adaptive strategy was beneficial for subjects participating the trial as it assigns doses to subjects based on the most recently updated data information.

Next, the Bayesian strategy used to update the parameters β_1, β_2 in Equation 1 is detailed. Based on the animal data, the least squares estimates of the intercept and slope parameters were obtained, and expressed by $\beta_{1, \text{animal}}, \beta_{2, \text{animal}}$ along with an estimate of the variance–covariance matrix Σ_{animal} . The Bayesian framework requires specification of a distribution for the data model, called likelihood, and a distribution for the model parameter, denoted as prior. For the example at hand, the likelihood conforms to the usual Gaussian likelihood whereby $\ln(\text{PGE}_2)$ was assumed to have a normal distribution with mean $\beta_1 + \beta_2 \text{ EPA:AA}$ and variance–covariance matrix Σ . Note that owing to the longitudinal nature of the data, the matrix Σ was not diagonal. The joint prior distribution of the model parameters, β_1, β_2 was assumed to be a bivariate normal with mean vector $\beta_{\text{animal}} = (\beta_{1, \text{animal}}, \beta_{2, \text{animal}})$, and variance–covariance matrix Σ_{animal} . Combined with the estimates from the first cohort of human data (i.e., $\hat{\beta} = (\hat{\beta}_1, \hat{\beta}_2)$ and Σ), the authors updated the parameter estimates, denoted by $\beta_{\text{post}} = (\beta_{1, \text{post}}, \beta_{2, \text{post}})$ given as:

$$\beta_{\text{post}} = \Sigma_{\text{post}}^{-1} (\Sigma_{\text{animal}}^{-1} \beta_{\text{animal}} + \Sigma^{-1} \hat{\beta}) \quad (3)$$

$$\Sigma_{\text{post}} = (\Sigma_{\text{animal}}^{-1} + \Sigma^{-1})^{-1}, \quad (4),$$

where the superscript -1 refers to matrix inverse operation. Equation 3 was referred to as the posterior estimate of β and is derived from a probabilistic calculation called Bayes formula. Equation 3 clearly points out that the estimate β_{post} was a weighted average of the prior estimate and human data estimate. The weights represent the relative precision in these estimates. It puts more weight on the human data as more and more human data become available. Although Equation 2 involves only the updated estimate of the slope, Equation 3 demonstrates that the estimates of both the intercept and slope from the previous stage play a role in such updates. Appendix 2 contains further details of the modeling process.

Mean reduction of target dose across cohorts were compared using two-sample *t*-tests. An assessment was made of the effect of the static strategy of dosing everybody based on the model obtained using animal data only. For each participant administered with updated dosing, authors compared his or her actual pill count with the pill count the participant would have been subjected to if dosing was determined only using data from the animal study. The average comparison was carried out using paired *t*-tests.

Subjects were enrolled in the study between 2013 and 2015, and the data analysis was carried out in 2016. All relevant statistical computations for this paper as well as the figures are produced in R, version 3.5.0 (codes are in Appendix 3).

RESULTS

The Bayesian strategy was applied to obtain the slope estimate used in Equation 2 to calculate the target EPA:AA, and subsequently used this to derive the target dose for each individual using the subject-specific dose–EPA:AA relationship. Based on data on 54 rodents, the slope was estimated to be -1.38 , and this estimate was updated after data were collected on ten subjects. The dosing model was calculated two more times, after data were accumulated on an additional eight and a further nine subjects. The posterior estimates of the slopes based on data from ten, 18, and 27 subjects, were -1.7 , -1.96 , and -2.03 , respectively (Figure 2 shows a graphical display). Putting these slopes into Equation 2, the offsets were obtained as 0.4, 0.35, and 0.34. As a result, models were not updated any further and the trial continued with the model developed with 18 human subjects in conjunction with the rodent data. In order to facilitate continuous enrollment into the study, additional subjects were dosed on the previous estimates while the dosing model was being updated. Consequently, at the end of the trial there were 16, 15, and 15 subjects who were dosed with respective estimates based on rodent data (Model 1), based on rodent data combined with ten additional subjects (Model 2), and the previous data with an 18 additional subjects (Model 3). The mean target dose decreased from 6.63 g/day with Model 1 to 4.06 g/day for the subjects dosed with Model 3 ($p=0.001$).

Apart from the first 16 subjects, all other subjects had received a target dose lower than that would have been administered using the animal-only model. For Model 2, the average reduction was 1.7 (SD=1.4) pills/day whereas for Model 3, the mean reduction was 1.38 (SD=0.8) pills/day. For either model, the mean reduction was statistically significant ($p<0.001$). Thus, the Bayesian design induced a significant decrease in pill burden for study participants.

DISCUSSION

The paper describes the nuances of the Bayesian methodology that was at the heart of a clinical trial aimed at reducing PGE₂ in the colon. The Bayesian design was implemented to facilitate a smooth, uninterrupted operation of the trial. The main purpose of the trial was to find an optimum personalized dose of a standardized omega-3 nutritional supplement to reduce the level of PGE₂ by 50%. This would allow for personalized risk-reduction dosing without requiring colonoscopy to measure colonic PGE₂. The target dose was personalized

during the trial through a dose–response curve that relied on blood fatty acid changes after short-term dosing with low and high omega-3 fatty acid doses, which allowed calculation of the target dose that was subsequently given for 12 weeks. EPA:AA ratios in serum were thereby utilized as a surrogate for measuring colonic PGE₂. The mathematical relationship between PGE₂ and this surrogate EPA:AA was critical in this process. The contribution of the Bayesian strategy established this relationship in an adaptive manner moving from an animal-only model to one mixed with human data. As more human data were collected, this method informed the dose-finding algorithm to incorporate the new information in a seamless manner. As shown in Equations 3 and 4, the final estimate was a weighted average of the animal and human data estimates with weights representing the relative precision in these estimates.

Figure 3 demonstrates the basic nature of the updates that underlies the Bayesian strategy. The four curves represent the posterior distributions for the slopes in Equation 1. Starting from the all-animal data (Model 1), the slope distributions shifted to the left, indicating sharper decline as information continued to be mixed from newly accrued human data. The near overlap between the last two curves lends further support to the decision of terminating the updates after Model 3.

The described strategy addresses a limitation of early-phase clinical trials with integral biomarkers that depend on data from animal models. It does not preclude the use of pharmacological paradigms that seek to translate animal data to human factors, but allows study designers to start at that translation, and, as human data accrue, to integrate those data into the conduct of the study. This may become more important in, for example, early phase trials of immunotherapies combined with adjuvant treatments (drugs or radiation), where the goal of the study is not to determine the maximum tolerable dose of the combination, but the minimum biologically effective dose of the adjuvant, potentially personalized to the patient.

Limitations

One limitation of the approach presented herein is, although it is assumed that the parameters associating the dose and response are different in animals and humans, it is also assumed that the parametric forms of the dose–response models in the animals and humans are similar, if not identical. As noted below, a power model might be employed to address this, although the additional parameter might slow the adaptation. Another known limitation is that rodent studies are based on very homogeneous populations, whereas human nutrition is notorious for its heterogeneity. Indeed, a primary finding of this trial was that, even though the Harris–Benedict dosing formula takes height and weight (and hence BMI) into account, the relationship between changes in serum EPA:AA and colonic mucosal PGE₂ differed between non-obese and obese participants. Though adaptation on potential confounders is probably not feasible for Phase II studies with modest sample size, Phase III trials using adaptive methodology could and should reassess the contributions of variables not considered in the in vivo studies.

The Bayesian estimates shrunk the animal model–based estimates at a rate proportional to the respective precision of the estimates from the animal- and human-only models. At the initial stages of the human trial, the estimates based on animal data tended to have more

precision (being based on larger amount of data), and consequently a higher weight. With the acquisition of more human data, the contribution from the animal data became less dominant.

CONCLUSIONS

In future work, an early termination point for the Bayesian updating needs to be defined so that the final model can be validated on a test set. To offset the higher weight corresponding to the animal data, one can conceive of an alternative strategy where the likelihood of the animal data is raised to a fractional power, α ($0 < \alpha < 1$), before augmenting it to a proper prior for the estimates. Such power priors are direct modifications of the one proposed by Ibrahim and Chen.²⁹ The Bayesian methodology described herein demonstrating translation of animal data to a clinical trial nonetheless can be utilized as a starting point for future trials that seek to optimize the dosing of a preventive or therapeutic agent for each individual.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(A)

(B)

Figure 1.

A schematic diagram of the dose-finding strategy.

Notes: Panel (A) shows how the targeted serum EPA:AA ratio was determined based on the ratio that is associated with a 50% reduction in colonic PGE₂. Panel (B) shows how the personalized dose of ω -3 fatty acids was established based on the relationship between serum EPA:AA ratios and colonic PGE₂.

PGE₂, Prostaglandin E₂; EPA:AA, Eicosapentaenoic acid: Arachidonic acid.

Figure 2.

Relationship between logarithm of colonic PGE₂ and serum EPA:AA ratios starting with rodent data only and updating the relationship with human data as it became available. PGE₂, Prostaglandin E₂; EPA:AA, Eicosapentaenoic acid: Arachidonic acid.

Figure 3.
Posterior distribution of slopes for the models shown in Figure 2.