Principal Investigator

First Name: Byron
Last Name: Vaughn
Degree: MD
Primary Affiliation: University of Minnesota
E-mail: bvaughn@umn.edu
Phone number: 6126258999
Address: VFW Cancer Research Center
406 Harvard Street, S.E. Mail code: 8036A
City: Minneapolis
State or Province: Minnesota
Zip or Postal Code: 55455
Country: United States
SCOPUS ID: 38962217000

2015-0527

General Information

Key Personnel (in addition to PI):   **First Name:** Andrew
Last name: Reinink
Degree: MD
Primary Affiliation: Minneapolis VA
SCOPUS ID: 56221927800

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

📄 bv_yoda_coi.pdf
📄 coi_-_ar.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00036439 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
NCT00096655 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
NCT00207675 - A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNF a Chimeric Monoclonal Antibody (Infliximab, REMICADE) in Pediatric Subjects With Moderate to Severe CROHN'S Disease
NCT00094458 - Multicenter, Randomized, Double-Blind, Active Controlled Trial Comparing REMICADE® (infliximab) and REMICADE plus Azathioprine to Azathioprine in the Treatment of Patients with Crohn's Disease

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Optimizing Infliximab in IBD: Developing a model to determine the optimal interval for monitoring infliximab concentrations

Narrative Summary:
Infliximab is an essential therapy for Inflammatory Bowel Disease (IBD). However the optimal dosing of infliximab remains uncertain. While historically dosed by weight, recent evidence suggests that dosing by trough concentration may improve outcomes and be more cost effective. We propose to use data from prior clinical trials involving infliximab in patients with IBD to build a model of infliximab use in an IBD population to determine the cost as well as optimal time for assessing and re-assessing drug concentrations. This model will help to determine the role of therapeutic drug monitoring for infliximab in people with IBD.

Scientific Abstract:
Background: Therapeutic Drug Monitoring (TDM), i.e. dosing based on drug trough concentration, in Inflammatory Bowel Disease has been proposed as the optimal way to dose infliximab. Retrospective and prospective trials consistently demonstrate that proactive TDM improves clinical outcomes including clinical remission. The cost of the test as well as optimal time to repeat the test is unknown and presents a barrier to TDM in the clinical setting.
Objective: To build a model of infliximab use in a population of patients with IBD to determine the cost effectiveness of TDM as well as to determine the optimal interval for repeat monitoring.
Study Design: We will construct a Markov model of disease progression and use it to simulate IBD patients progressing through disease states under different monitoring strategies (proactive TDM versus reactive TDM).
Participants: Data from published literature as well as clinical trial data (requested) will provide probabilities of passing through varying states in the model.
Main outcome measure: Main outcome measure is Quality Adjusted Life Year (QALY), overall cost, and relative cost effectiveness per each testing strategy. The secondary outcome will be optimizing the model to determine the best interval for TDM.
Statistical Analysis: Incremental cost-effectiveness ratio (ICER) will be calculated by dividing the difference in cost associated with each strategy by the difference in QALYs. Extensive one-way sensitivity analysis will be performed to determine the strength of the estimates and significant drivers in the model.

Brief Project Background and Statement of Project Significance:
The concept of Therapeutic Drug Monitoring (TDM) for biologics, predominately infliximab, is new in Inflammatory Bowel Disease (IBD). Traditionally infliximab was dosed based on weight. However anecdotal evidence and cross sectional studies soon demonstrated a clear association between infliximab trough concentration and clinical efficacy. Initially this led to "reactive TDM", i.e. checking infliximab trough concentrations only when a patient was failing the drug. Given the cost of infliximab, early identification of patients who are not likely to respond to further drug (such as those with adequate levels or those with high anti-drug antibodies) provided a way to individualize therapy, which proved to be cost saving (Velayos, Kahn et al. 2013, Steenholdt, Brynskov et al. 2014).

While reactive TDM for infliximab is an effective strategy, proactively TDM, i.e. monitoring drug concentration prior to loss of response, has been proposed as the optimal way to dose infliximab (Vaughn, Sandborn et al. 9000). A randomized controlled trial demonstrated that proactive measurement of infliximab improved clinical remission rates, but repeating the test within one year did not seem to improve outcomes further, although it appeared to be cost effective (Vande Casteele, Ferrante et al. 2015). Additional published data suggest that the true benefit of proactive TDM is likely to be after 1 year (Vaughn, Martinez-Vazquez et al. 2014). However much controversy remains about how to best implement proactive TDM. In an ideal situation, a patient on infliximab would have their trough concentration measured before their infusion, and their infusion adjusted based on that value. However the concentrations assay is expensive ($2,500 dollars from Prometheus Labs, San Diego) and can take about a week to return. Thus it is not practical to measure the concentration with every infusion.

Creating a Markov model of a population of patients with IBD starting infliximab will allow us to compare the cost effectiveness of testing strategies (proactive TDM versus reactive). Additionally this model will be able to inform how frequently testing is clinically useful. Published data typically does not have the information needed to create this type of model as it is often cross sectional in nature. However data from clinical trials where IBD patients received infliximab will allow us to calculate probabilities and rates of state transitions (e.g. having an acceptable trough concentration or developing antibodies to infliximab) necessary to create this model. Information from this study will directly impact patient care by providing clinicians evidence of the cost utility of TDM as well as understanding how often to monitor drug concentrations.

Specific Aims of the Project:
Specific Aim 1: To assess the cost effectiveness of proactively monitoring infliximab drug concentrations: A Markov model will be constructed to compare the quality adjusted life years of between two testing strategies. We hypothesize that proactively monitoring infliximab concentrations (proactive TDM) will be more cost effective than reactive testing.

Specific Aim 2: To determine the optimal interval for testing infliximab drug concentrations: We will develop a stochastic control optimization model to determine optimal or near-optimal policies for determining the frequency of monitoring anti-TNF antibodies and drug concentrations in patients with IBD on infliximab. We hypothesize that repeat testing at 12 months will have the greatest benefit.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Data sources will be clinical trials that have used infliximab in a population of patients with Inflammatory Bowel Disease. All patients with more than one infliximab concentration will be included to obtain the probability of achieving a given infliximab "state" over time. Infliximab states include the following: high level, therapeutic level, low level and positive antibody. The proportion of patients achieving those states over time will be used as the probability states in the Markov model. Both Crohn's disease and ulcerative colitis will be included. Subjects with only a single infliximab concentration will be excluded. Additionally subjects who recieved infliximab 10mg/kg initially will not be included into the primary analysis as the overall model will assume standard induction regimen of 5mg/kg.

Main Outcome Measure and how it will be categorized/defined for your study:
The main outcome measure for our study is the Quality Adjusted Life Years (QALYs) for two infliximab monitoring strategies: Proactive TDM or reactive monitoring (i.e. standard of care). We will calculate an Incremental Cost-Effectiveness Ratio (ICER) by dividing the difference in cost associated with each strategy by the difference in QALYs.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Infliximab concentrations will be categorized based on the following: High concentration, therapeutic concentration, low concentration, undetectable and positive antibody status. Relevant clinical data based on prior published works will inform these bins, a therapeutic concentration will be considered 5-10. The proportion of patients reaching

these various states over time from the various clinical trials will be used to determine the probabilities needed to develop the Markov model.

Changes to infliximab level based on increasing or decreasing infliximab dose will developed from prior published data as well as internally collected data from prior IRB approved study. QALYs and direct costs will be calculated based on 1 year time horizon and extrapolated to 3 and 5 years. The cost analysis will be performed from the third party payer and will include treatment and health state costs, but not indirect costs.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Clinical response will be defined at a decrease in 70 points in the Crohn's Disease Activity Index or decrease of 3 in the Mayo ulcerative colitis score. Analysis will be performed for IBD as a whole and pre-stratified based on Crohn's disease and ulcerative colitis. As immunomodulator therapy is known to decrease antibodies to infliximab and increase the infliximab concentration, the analysis will also be stratified based on immunomodulator status. Lastly infliximab dose is clearly related to infliximab dose which is dependent on patient weight. Infliximab dosing at 5mg/kg will be used as the standard reference dose at the start of the model.

Statistical Analysis Plan:
The requested data will be used as above to determine probabilities for achieving a given infliximab state over time. Dr. Vaughn, a clinical gastroenterologist with experience in TDM for infliximab in IBD will review the data from the request trials to determine the probabilities of achieving the various states. The Markov model and subsequent optimization model will be built by Dr. Enns. Dr. Enns is an Assistant Professor in the School of Public Health with experience in modeling for cost effectiveness.

For the cost effectiveness analysis the Markov model will be run repeatedly to simulate a population of patients with IBD. Dr. Enns will guide the analysis of costs and calculate the QALYs and ICER. Dr. Enns will also perform extensive one way sensitivity analysis to assess the strengths of the estimates and probabilistic sensitivity analysis to determine uncertainty in the model.

The optimization model will be a stochastic control optimization model to determine optimal or near-optimal policies for determining the frequency of monitoring anti-TNF antibodies and drug concentrations in patients suffering from IBD. The overall approach will be similar to that in (Negoescu et al. 2012). The model will find these policies by quantifying the existing trade-offs between less frequent monitoring - where costs are less but the risk to patient's health outcomes is significant - and more frequent monitoring . the model can maximize the net monetary benefit, defined as (QALYs) x (willingness to pay threshold) – (costs), taking into consideration the patient characteristics and treatment history.

Project Timeline:
Once granted, it is estimated that it will take 3-4 months to review the appropriate data and determine the appropriate infliximab state probabilities. At the same time, Drs. Negoescu and Enns will build the initial Markov model. Once the model is complete and appropriate probability states assigned, it will take 4 months to run and debug the model. Development of the manuscript will take another 3-4 months. This total process is likely to take 12 months.

Development of the optimization model will likely take an additional 6 months (which will overlap with the prior timeline), however access to data will not be needed for this as the probabilities from the first model will be used. If it appears more data collection is needed, then an extension will be requested between the initial 9 and 12 months.

Dissemination Plan:
It is anticipated that the cost effectiveness portion will be ready for publication in 9-12 months while the optimization portion will be ready in 12-18 months. The target audience includes gastroenterologists treating patients with Inflammatory Bowel Disease. Both manuscripts will be submitted to high impact gastroenterology journals such as The American Journal of Gastroenterology, Gut, Clinical Gastroenterology and Hepatology, and Inflammatory Bowel Diseases.

Additionally it is anticipated that early and preliminary results will be presented at the national GI conference (Digestive Diseases Week) in 2016.

Bibliography:

Negoescu, D. M., D. K. Owens, M. L. Brandeau and E. Bendavid (2012). "Balancing immunological benefits and cardiovascular risks of antiretroviral therapy: when is immediate treatment optimal?" Clin Infect Dis 55(10): 1392-1399.

Steenholdt, C., J. Brynskov, O. O. Thomsen, L. K. Munck, J. Fallingborg, L. A. Christensen, G. Pedersen, J. Kjeldsen, B. A. Jacobsen, A. S. Oxholm, J. Kjellberg, K. Bendtzen and M. A. Ainsworth (2014). "Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial." Gut 63(6): 919-927.

Vande Casteele, N., M. Ferrante, G. Van Assche, V. Ballet, G. Compernolle, K. Van Steen, S. Simoens, P. Rutgeerts, A. Gils and S. Vermeire (2015). "Trough Concentrations of Infliximab Guide Dosing for Patients With Inflammatory Bowel Disease." Gastroenterology.

Vaughn, B. P., M. Martinez-Vazquez, V. R. Patwardhan, A. C. Moss, W. J. Sandborn and A. S. Cheifetz (2014). "Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study." Inflamm Bowel Dis 20(11): 1996-2003.

Vaughn, B. P., W. J. Sandborn and A. S. Cheifetz (9000). "Biologic Concentration Testing in Inflammatory Bowel Disease." Inflammatory Bowel Diseases Publish Ahead of Print.

Velayos, F. S., J. G. Kahn, W. J. Sandborn and B. G. Feagan (2013). "A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab." Clin Gastroenterol Hepatol 11(6): 654-666.