

Principal Investigator

First Name: William J.
Last Name: Sandborn
Degree: M.D.
Primary Affiliation: University of California San Diego
E-mail: wsandborn@ucsd.edu
Phone number: 8586575284
Address: 9500 Gilman Drive
MC 0956
City: La Jolla
State or Province: CA
Zip or Postal Code: 92093
Country: United States
SCOPUS ID: 7102610425

2014-0287

General Information

Key Personnel (in addition to PI): **First Name:** Niels
Last name: Vande Casteele
Degree: Pharm.D., Ph.D.
Primary Affiliation: University of California San Diego
SCOPUS ID: 46261712700

First Name: Diane R.
Last name: Mould
Degree: Ph.D., FCP, FAAPS
Primary Affiliation: Projections Research Inc.
SCOPUS ID: 7004613680

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.

Project Funding Source: NVC is a Postdoctoral Fellow of the Research Foundation—Flanders (FWO), Belgium; grant number 1260714N

 [yoda_project_coi_form_for_data_requestors_sept_20141_wjs_nvc_drm.pdf](#)

Certification

Certification: Yes

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](#)

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

Research Proposal

Project Title

Post hoc analysis of the ACT-1 & ACT-2 trials to simulate individualized dosing regimens using a predictive model

Narrative Summary:

Anti-tumor necrosis factor (anti-TNF) therapy with monoclonal antibodies such as infliximab (Remicade®) has revolutionized the treatment of patients with inflammatory bowel diseases. Unfortunately 30% of the patients do not respond to anti-TNF therapy and of those initially responding, the risk for loss of response to the drug was reported to be as high as 40% when treated according to the standard dosing regimen. This can be attributed to suboptimal dosing and the development of antibodies towards the drug. A more rational way of dosing based on the exposure in the individual patient might overcome some of these challenges and prove to be more efficacious.

Scientific Abstract:

Background: The population pharmacokinetics (PK) of infliximab and the exposure-response relationship was described in patients with ulcerative colitis (UC). Given this causal relationship between infliximab concentrations and efficacy outcomes such as response, remission and mucosal healing, the use of therapeutic drug monitoring (TDM) was advocated as an approach to optimize infliximab therapy in patients with UC.

Objective: Our primary objective is to conduct an in silico study using a predictive model incorporating data from the ACT-1 and ACT-2 studies to identify appropriate dosing regimens in individual patients, in order to achieve a predefined infliximab concentration at a certain time point that correlates with an efficacy outcome.

Study Design: Retrospective in silico study.

Participants: Patients of the ACT-1 (NCT00036439) and ACT-2 (NCT00096655) clinical trials.

Main Outcome Measure(s): To identify the proportion of patients with UC needing non-standard (higher or lower) dosing of infliximab during induction or maintenance to reach effective infliximab concentrations that are associated with clinical response, mucosal healing and/or clinical remission.

Statistical Analysis: A predictive model incorporating previously published population PK models of infliximab will be used to predict the exposure-time profile in individual patients based on baseline covariates. The model can then be updated with individual serum drug concentrations using a Bayesian approach to refine the prediction.

Brief Project Background and Statement of Project Significance:

The population pharmacokinetics (PK) of infliximab was previously described in subjects with ankylosing spondylitis (1), ulcerative colitis (UC) (2) and Crohn's disease (CD) (3). Recently, the exposure-response relationship was described in subjects with CD (4) and UC (5). Given this causal relationship between infliximab concentrations and efficacy outcomes such as response, remission and mucosal healing, the use of therapeutic drug monitoring (TDM) was advocated as an approach to optimize infliximab therapy in patients with inflammatory bowel disease (IBD) (6). However, the high unexplained variability of infliximab PK in currently available population PK models makes it difficult to generate precise individual PK parameters which could introduce some challenges to the application of TDM in practice. It is therefore desirable to refine the existing population PK models to improve the precision of infliximab PK parameters in UC patients.

Recently, the principal investigators Dr. William Sandborn and Dr. Niels Vande Casteele in collaboration with Dr. Joseph Adedokun (employee of Janssen R&D) and in collaboration with Biotech Scientific Affairs, refined the existing PK model of infliximab for UC by incorporating time varying covariate values.

Given that the unexplained between subject variability of infliximab clearance remains moderately high despite the inclusion of multiple covariates, implementing TDM with infliximab may require a Bayesian approach whereby serum concentrations of infliximab measured after treatment are used to update individual PK parameters. This would allow constructing precise probabilistic models as a utility for physicians to guide dosing in the individual patient.

The results of this scientific exercise would be highly interesting for current clinical practice. Physicians face the challenge of treating patients with moderate to severe UC that do not respond, partially respond or initially respond but later lose response to infliximab. Given the absence of adequate biomarkers that can guide treatment decision

and dosing strategies, physicians are often left with a treat-to-symptoms approach which has been shown to be suboptimal, time consuming for the patient and costly. A predictive model could help physicians (based on patient- and disease-specific covariates) prior to initiation of infliximab therapy to identify 1) what is the ideal first dose and 2) what exposure over time profile is to be expected after this first dose in a given patient. Following measurement of the serum infliximab concentration in that patient, the model's parameter estimates and predictions can be refined and the physician can choose to adjust the dosing regimen accordingly. This will allow for tighter disease control, which we anticipate, will benefit patient's short- and long-term clinical outcomes.

In addition to improving the standard of care, this approach of dosing based on exposure can also aid in designing future clinical trials for new biologicals or post marketing trials for biologicals that are already on the market.

Specific Aims of the Project:

The main outcome of this project is to use a predictive model that could help clinicians to define the most optimal dosing regimen in an individual patient to target the recently establish exposure-response relationship cut-offs (5). Using baseline covariates of an individual patient in the model will return an initial estimate of several potential starting doses in that particular patient. This first estimate will be further refined by updating the system with time varying covariates and consecutive measurements of serum infliximab concentrations by Bayesian updating, so that a better prediction of the optimal dose for each individual patient can be achieved throughout the induction phase.

This predictive model will be used in silico on the patients of the ACT-1 and ACT-2 studies. This exercise will consist of calculating the most optimal start dose in these patients and to update the model using consecutive measurements of serum infliximab concentrations. For example how many patients achieved the target concentration at week 14 and how the model would have predicted to change the dose based on the week 8 infliximab concentration in those patients that did not achieve the target concentration at week 14.

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 that confirms or validates previously conducted research on treatment effectiveness

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

The dataset that will be used for the proposed analysis consists of 484 subjects from both ACT 1(C0168T37) and ACT 2 (C0168T46) Phase 3 studies.

Study C0168T37 (ACT 1) was a 54-week randomized, double-blind, placebo-controlled, parallel group study. Study C0168T46 (ACT 2) was a 30-week trial with similar design to ACT 1. Subjects were enrolled in each study with approximately equal allocation to placebo (Group I), infliximab 5 mg/kg (Group II) or infliximab 10 mg/kg (Group III). In ACT1, subjects in treatment groups II and III were to receive infliximab infusions at Weeks 0, 2, and 6, and at every 8 weeks up to Week 46 (i.e., Weeks 14, 22, 30, 38, and 46). In ACT 2, subjects in treatment groups II and III were to receive infliximab infusions at Weeks 0, 2, 6, 14, and 22.

The evaluable population for this analysis is defined as all subjects who received at least 1 dose of infliximab in ACT 1 or ACT 2 and who also had at least 1 measurable serum infliximab concentration record.

In order to utilize the predictive model, we would like to request to be able to use the data outside of the secure YODA data sharing platform. The data would be transferred to a separate secure Linux system which is running a web based package for dose individualization. The data would be uploaded into this system. Following completion of the evaluation, the data would be deleted from the system. Preferably, we would like to receive the data in Nonmem-format as we know the data have been formatted already by Johnson & Johnson to perform the initial infliximab population PK studies including time varying covariates. This will greatly facilitate data formatting for our project and would be the most time-efficient way.

Main Outcome Measure and how it will be categorized/defined for your study:

Primary outcome measure: The number of samples per subject needed to provide an accurate and precise estimate of future serum concentrations for each subject

Secondary Outcome Measures: The number of subjects who developed anti-drug antibodies and were predicted to need either a higher dose or a shorter dose interval or both. The number of subjects who were predicted to need either higher doses or shorter dose intervals or both who subsequently failed therapy. The number of subjects who were predicted to need either higher doses or shorter dose intervals or both and who responded to therapy. The number of subjects who were predicted to be adequately treated (e.g. concentrations at or above the specified

target) at the study dose who subsequently failed therapy. The number of subjects who were predicted to be adequately treated at the study dose and who responded to therapy. The number of subjects who could have had a dose reduction or a longer dose interval or both.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

In addition to the dosing regimen (dose and dose interval) and infliximab serum concentration, following covariates will be imputed in the predictive model:

- 1) Mayo score
- 2) Endoscopic score
- 3) C-reactive protein
- 4) Body weight
- 5) Albumin
- 6) Sex
- 7) Antibodies to infliximab
- 8) Concomitant medication

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Other covariates of interest are: age, disease duration, white blood cell count, hepatic enzymes (ALT, AST), hemoglobin, platelets, TNF-alpha, race, immune response, smoking history and extent of disease.

Statistical Analysis Plan:

The effects of patient factors on infliximab PK are described in previously published population PK models and allow for an initial estimation of the concentration-time profile based on individual baseline characteristics and the planned dose (2, 3). For our analysis we will use a recently published predictive model that refines that initial prediction by using Bayesian averaging, Bayesian updating and Bayesian forecasting techniques and also takes into account observed patient-specific drug concentrations to return a patient-specific dosing regimen (7) which has been shown to work well in other datasets (8). Applying a previously validated predictive model will allow a rapid initiation of the project.

The primary outcome measure will be tested using Liu's concordance criteria and calculation of the root mean square error. Bland Altman plots will also be generated.

The secondary outcome measures will be initially evaluated using summary statistics: For the univariate analysis of discrete variables, the Fisher's Exact or Chi-square test will be used where appropriate.

Project Timeline:

Start date: 1/4/2015 – end date: 31/12/2015. Data formatting: 0.5 month, data analysis using predictive model: 2 months, generating tables and figures: 1 month. Preparation of manuscript: 3 months. Anticipated date manuscript drafted and first submitted for publication: 1/11/2015. Anticipated date results reported back to the YODA Project: 31/12/2015.

Dissemination Plan:

Our findings of the application of the predictive model on the data from the ACT-1 and ACT-2 trial will be published in a high impact peer-reviewed journal. Suitable journals for submission of the completed research project: Gastroenterology, Gut, and American Journal of Gastroenterology.

Bibliography:

1. Xu Z, Seitz K, Fasanmade A, Ford J, Williamson P, Xu W, et al. Population pharmacokinetics of infliximab in patients with ankylosing spondylitis. *J Clin Pharmacol*. 2008;48(6):681-95.
2. Fasanmade AA, Adedokun OJ, Ford J, Hernandez D, Johanns J, Hu C, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol*. 2009;65(12):1211-28.
3. Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. *Clin Ther*. 2011;33(7):946-64.
4. Cornillie F, Hanauer SB, Diamond RH, Wang J, Tang KL, Xu Z, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. *Gut*. 2014.
5. Adedokun OJ, Sandborn WJ, Feagan BG, Rutgeerts P, Xu Z, Marano CW, et al. Association Between Serum Concentration of Infliximab and Efficacy in Adult Patients with Ulcerative Colitis. *Gastroenterology*. 2014.
6. Vande Castele N, Feagan BG, Gils A, Vermeire S, Khanna R, Sandborn WJ, et al. Therapeutic drug monitoring

- in inflammatory bowel disease: current state and future perspectives. *Curr Gastroenterol Rep.* 2014;16(4):378.
7. Xu Z, Mould D, Hu C, Ford J, Keen M, Davis H, et al., editors. A Population-Based Pharmacokinetic Pooled Analysis of Infliximab in Pediatrics. ACCP National Meeting; 2012; San Diego, CA.
8. Dotan I, Ron Y, Yanai H, Becker S, Fishman S, Yahav L, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis.* 2014;20(12):2247-59.