

Principal Investigator

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Project Title

Post hoc analysis of the ACT-1 & ACT-2 trials to develop a dosing calculator for infliximab for patients with ulcerative colitis

Research Proposal

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: To develop a calculator based on infliximab PK to optimize dosing in patients with UC and to conduct an in silico study based on a subset of patients of the ACT-1 and ACT-2 studies that evaluates how the dose should theoretically be adapted to achieve a predefined infliximab concentration at a certain time point that correlates with an efficacy outcome.

Study Design: Retrospective in silico study, translating pharmacokinetics and pharmacodynamics into a clinically applicable calculator.

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

Main Outcome Measure(s): A dosing calculator will be developed so that a better prediction of the optimal dose for each individual patient can be achieved. This calculator will be tested in silico using a subset of patients of the ACT-1 and ACT-2 studies.

Statistical Analysis: Using Nonmem® (Icon Development Solutions, Dublin, Ireland) software, the base PK model of infliximab for UC will be used together with Bayesian averaging, Bayesian updating and Bayesian forecasting techniques to develop the patient-specific dosing regimens.

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 (employer 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 BSV 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 calculator 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. Upon a consecutive measurement of the serum infliximab concentration in that patient, the model's prediction 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 of improving 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 develop a calculator that could help clinicians to define the most optimal dosing regimen in an individual patient to target the recently established exposure-response relationship cut-offs [5]. Imputing baseline covariates of an individual patient into the model will return an initial estimate of the optimal start dose in that particular patient. This first estimate will be further refined by imputing 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.

A secondary outcome will be to test *in silico* this approach on a subset of 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 calculator 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

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

Using Nonmem® (Icon Development Solutions, Dublin, Ireland) software, the base PK model of infliximab for UC will be used together with Bayesian averaging, Bayesian updating and Bayesian forecasting techniques to develop the patient-specific dosing regimens.

Our preference would be to perform this work in close collaboration with Janssen R&D and in particular with Dr. Joseph Adedokun (employer of Janssen R&D) as he has expert knowledge of pharmacokinetics/pharmacodynamics modeling as well as hands-on experience with the datasets.

This would allow a rapid initiation of the project, starting immediately from the base PK model of infliximab to construct the calculator. Access to the pharmacological data could be set up through Janssen R&D for the second stage of the proposal where we would do an internal validation of the calculator based on a subset of the ACT-1 and ACT-2 data. However, if such collaboration is not possible, then we are prepared to proceed with the analyses without collaboration.

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.

Project Timeline:

Start date: 1/1/2015 – end date: 31/12/2015. Development of calculator and data analysis: 9 months. Preparation of manuscript: 3 months. Anticipated date manuscript drafted and first submitted for publication: 30/11/2015. Anticipated date results reported back to the YODA Project: 31/12/2015.

Dissemination Plan:

The application of the dosing calculator on a subset of the data from the ACT-1 and ACT-2 trial will be published in a high impact peer-reviewed journal, with a functional calculator provider as a web supplement. Suitable journals for submission of the completed research project: Gastroenterology or Gut.

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;48:681-95.
- 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;65:1211-28.
- 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;33:946-64.
- 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 Casteele 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;16:378.

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

General Information

Key Personnel (in addition to PI): **First Name:** Niels
Last name: Vande Casteele
Degree: Pharm.D., Ph.D.
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SCOPUS ID: 46261712700

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

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

Conflict of Interest

COI Upload:  [yoda_project_coi_form_for_data_requestors_sept_20141_wjs_and_nvc.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