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General Information

Key Personnel (in addition to PI):
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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: The PhD of Violeta Balbas-Martinez is supported by a fellowship grant from the Navarra Government, Spain (BON 1132/2017)
How did you learn about the YODA Project?: Colleague

Conflict of Interest

http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2017_2-signed_inaki.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2017.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2018_vbm.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):

1. NCT01369329 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Have Failed

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

Research Proposal

Project Title

A Quantitative Systems Pharmacology Model for Crohn's Disease

Narrative Summary:

In our laboratory we have developed a Quantitative Systems Pharmacology (QSP) Model based on boolean interactions Balbas-Martinez V, et al.(1). Our current objective is to transform the qualitative model into a quantitative computational framework capable to describe the time course of different biomarkers and clinical outcomes during and after treatment in IBD patients, providing rationale for combination therapies. As our research is based on computational modeling, we do not have the possibility to set up clinical trials and have access to patients' data. That is why YODA initiative is key to achieve our research academic goals.

Scientific Abstract:

BACKGROUND
Inflammatory Bowel Disease's (IBD) complexity, with many altered molecular pathways, is likely to be the reason behind the lack of an effective therapy, which currently exerts symptomatic rather than curative effects (2). There is an urgent need for integration of available mechanistic knowledge into computational frameworks providing new hypothesis, drug combination strategies, new target identification and patient stratification. We integrated IBD knowledge in a network model identifying key players and connections, allowing to understand IBD as a system (1).
OBJECTIVE
To develop and validate a quantitative model incorporating mechanisms (and so, cellular and protein components) key for Crohn´s disease.
DESIGN
The data will be explored (descriptive statistics) and integrated in the model. Constrains will be generated to apply optimization techniques for parameter calibration. Model evaluation will be done with the data.
PARTICIPANTS
Both, placebo-controlled and parallel-group patients enrolled in the NCT01369329 trial.
OUTCOMES
A computational platform able to (i) describe the clinical response for different therapies and explore in silico alternatives to improve the clinical outcome, (ii) be reduced to estimate parameters and inter-individual variability (3), dosing individualization or design new experiments in clinic or by the pharmaceutical industry.
STATISTICAL ANALYSIS
Selection between competing models and model performance will be evaluated based on standard methods used in Systems pharmacology (4) and population PK/PD modeling (5).

Brief Project Background and Statement of Project Significance:

Literature on complex diseases is abundant but not always quantitative. Specially, in Inflammatory Bowel Disease (IBD), many molecular pathways are qualitatively well described, but this information cannot be used in traditional quantitative mathematical models employed in drug development. The success of an IBD therapy depends on a balanced response of the immune system against the bacterial dysbiosis and the inflammatory signals(6). Under these circumstances, proper understanding of the dynamics of the immune response is essential to identify potential therapeutic targets and biomarkers that predict responses to current or future therapeutic approaches,

especially those based on drug combinations. At this point, computational modeling is critical to integrate available information and data into a mathematical framework that can describe and predict the outcome of different therapeutic alternatives, identify potential new targets, and evaluate different dosing scenarios of currently available therapies.
In this regard, different efforts have been undertaken to model individual aspects of the immune response in IBD, mainly differing on the level of information included in the model (bacterial dynamics, innate response, cellular response, etc.) (7)(8). Nevertheless, these models lack of a holistic and/or mechanistic understanding of main components of the immune system and the interaction among them.
Given the fact that currently longitudinal data associated with the most relevant elements of the system are extremely scarce, the objective of this request is to acquire data from Crohn´s patients to validate(confirm) mechanism-based hypothesis of a systems pharmacology model constructed base on literature data. Those data will also dictate the degree of model reduction with the goal of making the system applicable to fit/describe data from clinical trials.
This project, is involved inside the MID3 approach(9), combining several methodologies such as Systems Pharmacology (SP) and Pharmacokinetics/Pharmacodynamics and Model and Simulation (PKPD&MS) constituting one of the cutting edge initiatives for personalized medicine and target selection.
In case of successful application, the systems pharmacology model developed with the data provided will not be placed on hold waiting from further developement. It will be shared with the community in different specialized conferences. In fact, the computational related research is finished (1,10), and it has been presented at the Population Approach Group in Europe 2016 and 2017 (11–13) and at the International Conference on Systems Biology 2016 conferences(14). Additionally, in a recent collaboration with the Iowa State University, this SP model for IBD was used to simulate the effect of a non-competitive antagonist of the purinergic receptor P2X7 and guide dose selection for an upcoming clinical study in IBD in dogs. The model used inflammatory biomarkers IL-1b and IL-18 as well as the tissue damage biomarkers metalloproteinases as surrogate end points of efficacy. These findings will now inform the design of a proof-of-concept study in IBD dogs prior to clinical development in human(15).

Specific Aims of the Project:

Once we have developed a mechanistic model including the key elements and pathways involved in the progression of the IBD disease, the data obtained through the YODA initiative will be used to: (i) execute the external validation of the mechanistic model (ii) revise principal model assumptions, (ii) Evaluate in silico potential combinations using the response readouts of the NCT01369329 trial as reference, (iii) Reduce the dimension of the systems pharmacology model so that it can handle data from clinical trials allowing to estimate model parameters and its magnitude of inter-individual variability, (iv) Optimize dose and dosing regimens and experimental designs of both in vitro and in vivo studies and clinical trials.

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 populationsConfirm or validate 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:

We seek for individual Participant-Level Data enrolled in the UNITI-1 trial, which includes Full CSR and all supporting documentation and especially, detailed dosing information and administration schedule, as well as mode and route of administration, and type of pharmaceutical formulation, and patient characteristics (such as sex, age, weight, height, comorbidities, creatinine clearance, any genotype information and disease status).
Longitudinal data of drug exposure (i.e., drug concentrations in plasma), biomarkers (different cytokines such as TNFa, IFNg, IL17, IL10, IL12, IL23, IL6, TGFb, IL1b, IL22...), and clinical readouts (CRP, Calprotectin or Metalloproteinases) are essential as they make possible the change from standard statistics metrics to a mechanistic computational modeling as our approach relies on availability of data capable to “speak” about key processes involved in drug response and progression of the disease. The model components intended to be included in the mechanistic model can be seen in the attached document called "IBD QSP Model components.docx".

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

We will provide to the scientific community with (i) an initial Quantitative Systems Pharmacology (QSP) model able to characterize the dynamics of the main immunological components in Crohn´s disease. We will base the model building process on a Gadkar, K et al.,(16) manuscript which presents a conceptual workflow supporting a robust application of QSP. As the final step of model building, we will be able to quantitatively describe the typical profile of the Crohn´disease components "IBD QSP Model components.docx" and relate therapy simulation outcome to a disease score. (ii) Afterwards, we will provide with a reduced version of the model, ready to be used to design new trials (number of samplings) or define key biomarkers during early therapy decision making.

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

So far, the main predictor variables are dose, dosing schedule and the type of therapeutic agent. Therefore, we move from these standard predictors to a more mechanistic wise biomarkers downstream (i.e., cytokines). We constrain ourselves with those that are currently easily measured in circulating blood.
One of the main readouts of our study would be, in addition, to find the most relevant biomarker/s to predict drug response and therefore, the link between those biomarkers and the response, through different approximation such as hazard ratio or odds ratio.

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

To stablish the mechanistic link between drug exposure, immunological pathways, biomarkers and response, other variables that we are interested in could be patient characteristics. As recorded in this list, patient characteristics, either during the trial or at baseline, could affect those mechanisms. Therefore, status of the disease, genotypes or basal cytokines levels could be relevant for our model building process.

Statistical Analysis Plan:

Our objective is not the re-evaluation of the primary end points of the clinical trial. In this sense, we do not plan any statistical analysis of the data per se. The analysis in the first part of this project, would be oriented to evaluate the prediction capacity of the model based on the clinical trial characteristics (dose, dosing schedule, initial cytokines levels and any other useful available information). As the model would be pure mechanistic, we intend to capture not only the replication of the he species dynamic (interleukins) after therapy simulation with our model (given a known dose and dosing schedule of the monoclonal antibody) but also a decrease in our mechanistic in silico disease score. This reduction on our simulated disease score would not be a re-evaluation of the primary endpoints of the provided study, but a confirmation of our model success.

One of the last phases of our planed project corresponds to model reduction. Once we had achieved the aforementioned goal, we would use the trial data for parameter estimation and we then would use the standard statistics on this modeling approach, such as the Log-likelihood profile or visual predictive checks (VPC) for parameter precision(17).

Project Timeline:

Once approved we anticipate:
-1 month for data collection and review.
-4 months for model validation and refinement
-3 months for model reduction.
-2 months for population PKPD modeling applying the reduced model
-2 months for manuscript(s) written and preparing the report

Dissemination Plan:

It is estimated to obtain between one and two publications from this work one would include the complete QSP model for Crohn´s disease, and the second would correspond to the reduced model. Some potential journal for publication could be Clinical Pharmacology & Therapeutics, Clinical Pharmacokinetics or other high impact factor journal. The target audience for this work includes Pharmacometricians, Immunologist and Inflammatory disease specialists from the industry, academic and clinical setting. This topic is particularly of interest as SP is an emergent concept that is becoming more popular given the richness of information that these models contain. As in academy the data availability is very scarce, this approach needs collaboration with external institutions able to

provide the necessary data to develop useful models and create innovative and promising knowledge to advance in the right direction through new discoveries. As this topic has received much attention at recent international conferences (11–14), the preliminary results would be presented as a poster or conference at the PAGE meeting, at the ACoP or at the Crohn's & Colitis Congress, not only to show the results, but also to provide an example of what can be done with already existing knowledge and very few resource

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Supplementary Material:

ibd_qsp_model_components.docx cd_qsp_model_output.docx