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NCT00267969 - C0743T08 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo Controlled Trial Evaluating the Efficacy and Safety of Ustekinumab (CNTO 1275) in the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis
NCT00307437 - C0743T09 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Evaluating the Efficacy and Safety of CNTO 1275 in the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis
NCT01550744 - CNTO1275PSO3009 - A Phase 3b, Randomized, Double-blind, Active-controlled, Multicenter Study to Evaluate a "Subject-tailored" Maintenance Dosing Approach in Subjects With Moderate-to-Severe Plaque Psoriasis
NCT02203032 - CNTO1959PSO3003 - A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of Guselkumab for the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis and an Inadequate Response to Ustekinumab
NCT00454584 - C0743T12 - A Phase 3, Multicenter, Randomized Study Comparing CNTO 1275 and Etanercept for the Treatment of Moderate to Severe Plaque Psoriasis
NCT01059773 - CNTO1275PSO4004 - An Exploratory Trial to Assess Naturalistic Safety and Efficacy Outcomes in Patients With Moderate to Severe Plaque Psoriasis Transitiioned to Ustekinumab From Previous Methotrexate Therapy (TRANSIT)

Principal Investigator

First Name: Robert
Last Name: Gniadecki
Degree: Doctor of Medicine
Primary Affiliation: University of Alberta, Department of Medicine & Dentistry, Division of Dermatology
E-mail: surmanow@ualberta.ca
Phone number: 587-889-2809
Address: Division of Dermatology. 8-112 Clinical Science Building, 11350-83 Ave, Edmonton, Alberta, T6G 2G3, Canada

City: Edmonton
State or Province: Alberta
Zip or Postal Code: T6G 2G3
Country: Canada
SCOPUS ID: 7005836029

General Information

Key Personnel (in addition to PI):

First Name: Philip
Last name: Surmanowicz
Degree: Bachelor of Medicine
Primary Affiliation: University of Alberta, Division of Medicine & Dentistry, Department of Dermatology
SCOPUS ID:

First Name: Sepideh
Last name: Emam
Degree: PhD
Primary Affiliation: University of Alberta - Canada
SCOPUS ID:

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/phil_coi-merged.pdf
https://yoda.yale.edu/system/files/robert_coi-merged.pdf
https://yoda.yale.edu/system/files/coi-sepideh.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

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

Research Proposal

Project Title

Alternative Data Presentation For Treatment Outcomes in Psoriasis

Narrative Summary:

Modern patient care is built upon evidence-based medicine and relies on clinical trial data. However, traditional outcomes such as proportions of patients achieving a primary outcome lack clinical relevance for physicians. This project will investigate the usage of alternative methods of data analysis and presentation focusing on capturing individual patient outcomes, such as: waterfall plots and spider plots. We will also explore a Bayesian aggregate n-of-1 design in psoriasis biologic clinical trials to describe individualistic therapy outcomes. We hypothesize these methods will provide more clinically relevant information and facilitate psoriasis treatment decisions for clinicians.

Scientific Abstract:

Background:
Psoriasis clinical trials have traditionally used Psoriasis Area and Severity Index (PASI) scores as a primary outcome and reported proportions of patients achieving PASIs reduction in a frequentist statistical model (group comparison). A more informative method of data presentation for the clinician would be in terms of probability for treatment success in the best and worst cases.
Objective:
-Can alternative data presentations and analyses improve conclusions and information provided from psoriasis biologic clinical trials?
-Can a Bayesian aggregate n-of-1 approach limit sample sizes and enable the design of more cost-effective trials?
Study Design:
We will re-analyze raw psoriasis clinical trial data and generate waterfall plots illustrating PASI or Dermatology Quality of Life Index (DLQI) improvements, spider plots assessing long-term drug efficacy, and a Bayesian aggregate n-of-1 format to generate a posterior probability distribution for the probability of achieving a PASI75 score.
Participants:
We will include patients with plaque psoriasis that were included in the phase III trials: NCT00267969, NCT00307437, NCT00454584, NCT01059773, NCT01550744, NCT02203032.
Main Outcome Measure(s):
1) Distribution of individual PASI and DLQI responses in participants receiving biologic treatment for psoriasis.
2) Modeling of the sample size effect using n-of-1 design and Bayesian hierarchical model meta-analysis.
Statistical Analysis:
Bayesian analysis n-of-1 design as described by 1-3.Alternative data models will be prepared using R suite.

Brief Project Background and Statement of Project Significance:

Clinical trial data form the empirical foundation for modern evidence-based medicine. Through this process, drugs are rigorously studied for their safety and efficacy before recommendations may be formed to guide clinical decision-making. Just as the therapeutic options for psoriasis continue to develop and improve, so too must the analysis and data presentation models used to generate and illustrate trial results.

Current PASI score and frequentist methods do not visualize the entire spectrum of individual patient responses. Current developments in other fields such as in oncology advance towards alternative methods of data visualization encompassing the responses in the entire study population. Examples are the spider and waterfall plots that illustrate each patient’s unique drug response rates as well as population response distributions. Waterfall plots demonstrate the entire cohort’s response distribution to treatment by illustrating each patient’s individual response, effectively resulting in a waterfall-like figure 4,5. Spider plots have been used in oncology publications to graph tumor size changes longitudinally over time 4. We hope to extend this functionality into the field of dermatology and assess long-term biologic efficacy for treatment and maintenance of psoriasis. Ultimately, we aim to explore the usage of such alternative data presentation methods, improve the external validity of psoriasis drug studies, and optimize patient-care by providing practitioners with more complete results and conclusions. Furthermore, the implementation of more individual-centered data presentation may facilitate future studies exploring personalized medicine and enable researchers to inquire into what factors lead to a single patient’s unique responses to various psoriasis biologics.

Bayesian aggregate n-of-1 formats have previously been used in studying rare disease treatments where gathering high-quality treatment evidence is challenging due to limited resources, insufficient patient populations, and considerable heterogeneity 1. In extending this methodology into psoriasis biologic clinical trials, we hope to enable the design of smaller and more cost-effective studies with comparable outcomes to larger clinical trials. We will make use of previous published protocols as a reference when designing our own Bayesian aggregate n-of-1 analyses 1-3.

This study is original and the proposed methods for data analysis and visualization have not been attempted before for psoriasis.

Specific Aims of the Project:

The aims of this project are to:
-Explore whether alternative data presentation and analysis methods, such as spider and waterfall plots, could be utilized to add to the conclusions and information provided from psoriasis biologic clinical trials.
-Explore whether a Bayesian aggregate n-of-1 approach could limit sample size and enable the design of more cost-effective.

We hypothesize that incorporating spider and waterfall plots will prove valuable for illustrating individual patient response and population response distributions, and could be utilized to improve clinical decision-making. We also believe implementing a Bayesian aggregate n-of-1 approach to psoriasis biologic clinical trials could provide similar conclusions to traditional larger trials.

What is the purpose of the analysis being proposed? Please select all that apply.
Confirm or validate previously conducted research on treatment effectiveness
Preliminary research to be used as part of a grant proposal
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project

Research Methods

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

We will include patients with plaque psoriasis that were included in phase III clinical trials. Both placebo-controlled trials and trials with active comparators will be included. The list of trials are as follows: NCT00267969, NCT00307437, NCT00454584, NCT01059773, NCT01550744, NCT02203032. There are no other exclusion criteria.

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

The main outcomes are 1) individual reduction of PASI scores over time and individual reduction in DLQI scores and 2) absolute values pf PASI and DLQI at all timepoints during treatment.
Secondary outcomes are 1) proportions of patients achieving PASI and DLQI reductions by 50%, 75%, 90%, and 100%, 2) proportion of patients achieving predetermined PASI values 0, <2, <5, 5, and 3) proportion of patients achieving DLQI values of 0, <2, and <5.

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

-Failure of previous biologic therapy (yes/no).

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

-Sex (male/female)
-Body weight, body mass index, or presence of obesity (as available)
-Presence or absence of psoriatic arthritis (yes/no)

Statistical Analysis Plan:

-Individual data (primary and secondary outcomes) will be plotted using R-scripting to visualize individual responses using waterfall plots (single endpoint) and spider plots (multiple endpoint in time) for different studied drugs and placebo. Further statistical analysis will be descriptive by analysing the overall shape of the curves and presence or absence of the visually obvious thresholds in the level of population responses.
-Depending on the results of this analysis, we would like to reserve the right for other types of data presentation, if applicable (e.g. movies showing longitudinal variability in clinical responses).
-For the Bayesian analysis, the independent variables listed above will be used as priors. In this analysis, we will include patients who received more than one block of therapy (e.g. active treatment and placebo). Individual patients will be treated as trials and analysed using meta-analysis methodology described by Chen and Chen2. We will use modelling with different numbers of patients (n=10, 15, 25, 50, 100) to analyse the sample size of individual patient trials that give equivalent statistical results to the frequentist analysis (methodology is described in reference

1). The response will be presented as the probability curve of achieving a predetermined outcome: PASI75 or PASI90 (this outcome will be the same as the primary or secondary outcomes in the original study).
Software Used:
R

Project Timeline:

The project will begin as soon as we have access to the clinical trial data. We will aim to have applied, and have access, to the raw clinical trial data by the end of April. Next, we will re-analyze the data and prepare waterfall plots illustrating PASI or DLQI improvements and spider plots assessing long-term drug efficacy – this should be completed by the end of June. We hope to have the Bayesian aggregate n-of-1 data prepared by the end of July. Both of the above steps constitute our planned analyses. August and September will be spent interpreting our prepared data presentation models and preparing the discussion and conclusions. The final six months of our 12-month data usage will be dedicated to preparing the manuscript for publication. We plan to have a draft ready for publication by the end of December 2019.

Dissemination Plan:

We plan to publish the results in peer-reviewed dermatological journals. Potentially suitable target journals are, but not restricted to: J Am Acad Dermatol, Br J Dermatol, JAMA Dermatology.

Philip will apply to present the results, once published, at the Canadian Dermatology Association 2020 conference, the Skin Research Group of Canada 2020 conference, the Society of Investigative Dermatology 2020 conference, and the University of Alberta 2020 Day of Medical Research Symposium.

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