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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: National Institute of Health Research, UK
How did you learn about the YODA Project?: Internet Search

Conflict of Interest

http://yoda.yale.edu/system/files/yoda20project20coi20form20for20data20requestors.docx
http://yoda.yale.edu/system/files/yoda_coi_0.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. NCT00267969 - 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
2. NCT00307437 - 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

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

Research Proposal

Project Title

Comparison of “real-life” clinical practice to clinical trials– a propensity score standardization method

Narrative Summary:

Patients from clinical trials for biologic treatment of psoriasis may not be representative of the population treated in the real world. There is preliminary evidence that patients ineligible for clinical trials have a greater risk of adverse event from treatments. To define how differences between the real world and the clinical trials impact on results from the evaluation of treatments for psoriasis, we aim to look at changes to outcomes of treatment effectiveness and safety from a large national patient registry in the UK - the British Association of Dermatologists Biologic Interventions Register - after standardising this group of patients to a clinical trial population.

Scientific Abstract:

Background:
Patients enrolled in pivotal licensing trials for biologic treatment of psoriasis may not be representative of the population treated in real life. There is preliminary evidence that patients ineligible for clinical trials have a greater risk of adverse events.

Objective:
To quantify the difference between treatment effectiveness and safety outcomes between the clinical trial population and a real-world patient population

Study Design:
Observational prospective cohort study

Participants:
Participants from the British Association of Dermatologists Biologic Interventions Register (BADBIR); Participants from two pivotal licensing clinical trials for ustekinumab in the treatment of psoriasis

Main Outcome Measures:
Incidence rate of serious adverse events (SAEs) in population on biologics and systemic non-biologics from BADBIR
Absolute Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index 0 or 1 at 6 months from BADBIR

Statistical Analysis:
The above outcomes will be estimated in a propensity score inverse probability treatment weighted population from BADBIR. The BADBIR population will then be reweighted using the baseline characteristics distribution from the clinical trial population, using propensity score “Standardised mortality ratio” (SMR) method. The risk and effectiveness outcome estimates from the new Trial weighted population will be obtained, and differences between populations quantified using absolute risk and relative risk measures (odds ratio/hazards ratio).

Brief Project Background and Statement of Project Significance:

The British Association of Dermatologists Biologics Interventions Register (BADBIR) is a national prospective safety register created to ascertain the risk of biological therapy in psoriasis. The design of BADBIR (1) and the baseline patient characteristics (2) have been published previously. This longitudinal observational study, established in 2007 by the BAD, is a comprehensive register of patients receiving biologic therapy for psoriasis. A cohort of patients on non-biologic systemic therapies (comparator cohort) is included in BADBIR to whom adverse event rates can be compared. The National Institute for Health and Care Excellence (NICE) recommended that all patients in the UK receiving biologic therapies for psoriasis should be registered with BADBIR, providing an

exhaustive pharmacovigilance service for post-marketing safety surveillance. To date, over 12000 patients have been recruited from 153 patient centres in the UK. As such, data from BADBIR has high external validity.

Although it is widely known that data from clinical trials has limited external validity due to strict inclusion and exclusion criteria, the magnitude of difference between outcomes seen in clinical trials to that of the real-world in patients with psoriasis on treatment is poorly quantified. A recent study using observational data from a psoriasis pharmacovigilance register compared the risk of serious adverse events associated with systemic therapies for psoriasis in a group of patients who would have been ineligible for RCTs against a group of patients who were eligible (3). The ineligible group, which represented 30% of the overall pharmacovigilance population, had an increased risk of serious adverse events. However, this study was limited by the fact that full study protocols were not available for all the licensing trials, limiting the ability for the study team to fully take into account the true inclusion and exclusion criteria employed for these trial studies. Furthermore, it was not able to investigate outcomes of effectiveness, nor take into account more subtle selection bias that may have been employed by both clinicians recruiting into trials and the patients themselves.

Quantifying the difference between trial and real-world population will help both clinicians and patients infer results from clinical trials to real-world settings, and take into account the intrinsic difference between the populations that may have affected the estimate. It may also focus researchers to use observational data for research where there is a substantial difference between these populations, and avoid research questions where there is little difference, reducing research waste.

Specific Aims of the Project:

The aim of the project is to answer the question: How does the safety and effectiveness estimates from a real-world registry compare to what would have been achieved if the registry was composed of a psoriasis clinical trial population? The study objective is to quantify the difference between treatment effectiveness and safety outcomes between the clinical trial population and a real-world patient population. The hypothesis is that there will be a substantial and clinically meaningful increase for effectiveness measures, and a clinically important decrease for adverse event measures seen in the real-world population when this is standardised for the clinical trial population.

What is the purpose of the analysis being proposed? Please select all that apply.
Research that confirms or validates previously conducted research on treatment effectivenessResearch that confirms or validates previously conducted research on treatment safety

Research Methods

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

Data source for real-world population will be from BADBIR.
Inclusion Criteria will be patients who have had 1 or more follow-up registered within BADBIR, on either a biologic therapy (adalimumab, infliximab, etanercept, ustekinumab, secukinumab, inclusive of biosimilars) or a non-biologic systemic therapy (methotrexate, ciclosporin, fumaric acid esters, acitretin, PUVA, hydroxycarbamide, apremilast).
All patients from the clinical trials will be included for the individual patient baseline characteristic data to calculate the SMR weighting.

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

The main outcome measures are:
1. Incidence rate of SAEs over all follow-up time
2. Hazard ratio of SAEs against non-biologics
SAEs are adverse events that are associated with hospitalisation; intravenous therapy; or death.

3. Absolute PASI 0 or 1 at 6 months (approximates to PASI 90)
4. Odds ratio of achieving absolute PASI 0 or 1 at 6 months against non-biologics
5. DLQI 0 or 1 at 6 months
6. Odds ratio of achieving absolute DLQI 0 or 1 at 6 months against non-biologics

These measures will be obtained before and after SMR weighting for trial population.

Secondary outcome measure will include absolute PASI 3 or below as an approximation to PASI 75.

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

All patient baseline characteristics that are common to both the BADBIR and the requested trials (PHOENIX 1 and 2) will be included in the calculation of a propensity score (propensity for being selected for the clinical trial). Variables projected to be included in the calculation of the propensity score include: age, sex, weight, duration of psoriasis, PASI, DLQI, patients with psoriatic arthritis, previous treatment history, patients with previous tuberculosis.

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

Any other variable that is collected in both the BADBIR and the clinical trials patient population will be included in the calculation of the propensity score and the standardisation weighting.

Statistical Analysis Plan:

Descriptive analyses of the patient characteristics that are collected in the BADBIR and the clinical trial populations will be performed.

Crude incidence rates for the biologic cohort and the non-biologic cohort for SAEs will be calculated as the number of events per 100 patient-years of follow-up. Survival modelling with Cox proportional hazards before and after adjustment by propensity score (propensity for treatment with a biologic) will be used to compare event rates. Inverse probability treatment weighting (IPTW), where the treatments were weighted for the distribution of the propensity score in the whole model cohort, will be used. Balance between groups after weighting will be assessed using expected bias from a logistic regression model estimating the effect of the variable on serious infection.

Absolute PASI 0 or 1 at 6 months and DLQI 0 or 1 at 6 monthswill be calculated for effectiveness measures. Logistic regression will be used to obtain odds ratio of achieving absolute DLQI 0 or 1 at 6 months against non-biologics and of achieving absolute PASI 0 or 1 at 6 months against non-biologics, with adjustment by propensity score IPTW performed as above.

Individual patient-level data from the trials will then be used to calculating a different propensity score after both baseline populations are combined, using propensity for getting into a trial. The BADBIR population will be weighted on the trial population distribution using propensity score “Standardised mortality ratio” (SMR) method. The risk and effectiveness outcome estimates from the new Trial weighted estimates will be recalculated and compared to the original BADBIR population weighted estimates, and from any difference infer the gap between trial and real-world population.

We propose that the IPD data be allowed to be downloaded onto a University of Manchester computer. Data will be accessed by the PI only. STATA will be used as the statistical software of choice for the analyses. This is due to the fact that BADBIR data is restricted for use within the University of Manchester.

Project Timeline:

Application submitted to YODA: 12/05/2017
Approval from YODA: 12/06/2017
Project start date: 01/07/2017
Analysis completion date: 01/10/2017
Date manuscript drafted: 01/12/2017
First submitted for publication: 22/01/2018
Date results reported back to YODA project: 22/01/2018

Dissemination Plan:

As the paper in bibliography 3 is highly cited within the dermatology literature, it would be anticipated that the manuscript from this study would be equally if not more highly cited given the quantification of difference between real-world and trial populations in IPD baseline characteristics, and also both safety and effectiveness outcomes.

We anticipate an original research paper reporting the findings that would also be submitted in abstract form. We plan to submit an abstract summarising the data to the International Investigative Dermatology meeting in 2018. We believe that this data will be of interest across different target audiences, e.g. dermatologists; clinical researchers; researchers interested in evidence based medicine; and researchers interested in biologic safety research.

Expectation for study manuscript journal submission: dermatology journal e.g Journal of Investigative Dermatology, British Journal of Dermatology / or pharmacoepidemiology journal e.g. Pharmacoepidemiology and Drug Safety

Bibliography:

(1) Burden AD, Warren RB, Kleyn CE, McElhone K, Smith CH, Reynolds NJ, et al. The British Association of Dermatologists' Biologic Interventions Register (BADBIR): design, methodology and objectives. Br. J. Dermatol. 2012;166(3):545-54
(2) Iskandar IY, Ashcroft DM, Warren RB, Yiu ZZ, McElhone K, Lunt M, et al. Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. Br. J. Dermatol. 2015;173(2):510-8
(3) Garcia-Doval I, Carretero G, Vanaclocha F, Ferrandiz C, Dauden E, Sanchez-Carazo JL, et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Arch. Dermatol. 2012;148(4):463-70

Supplementary Material:

yoda_project_research_proposal_direct_data_access_badbir.pdf

responses_to_request_for_additional_information.docx