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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: Innovative Medicines Initiative (IMI) 'BeTheCure' project which is part of the European Union's Seventh Framework Programme (FP7/2007-2013) www.imi.europa.eu
How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_nnc_signed_0.pdf

http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_rw_signed_0.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2016_mhb_signed_0.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2017_tm_signed.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. NCT00269867 - A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody (cA2) in Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment

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

Research Proposal

Project Title

From clinical trials to routine care: understanding patient response to biologics in rheumatoid arthritis.

Narrative Summary:

This project will ask if clinical trial results apply to the more varied routine-care rheumatoid arthritis population, as recorded in a national UK registry. If not, can registries provide more useful information on patient response to drugs? We will investigate differences between trial patients and registry populations and assess whether treating more varied patients compared to trials, leads to less benefit and less/greater risk. This project will create a new method of assessing drugs based on the characteristics of patients and provide guidance to improve patient care and benefit.

Scientific Abstract:

Background: Randomised controlled trials are the gold standard for evaluating efficacy of new therapies. Their strict eligibility criteria limits their generalisability to real-world populations, which is represented in registries. Registry data can complement the evidence from trials but methods to best achieve this are lacking. Objectives: To develop a novel method to maximise the clinical utility of existing registry data. This will allow the comparison of baseline characteristics and clinical response in trial patients with those from routine-care, and evaluate associations between them to establish the degree of applicability of trials to a standard UK patient population. Also, to explore if there are differences between individual-patient data (IPD) and summary patient data (SPD) from trials when comparing outcomes with the routine-care population. Study design: Retrospective methodological study. Participants: Patients with rheumatoid arthritis receiving infliximab after conventional disease-modifying anti-rheumatic drugs failure enrolled in the UK-based biologics register and the ATTRACT trial. Main Outcome Measures: The difference in the proportion of patients with a 20% improvement in their clinical response between the trial and registry populations at 12 months. Statistical Analysis: Matching algorithms will be developed to simulate a trial environment within the UK registry by using both IPD and SPD from the ATTRACT trial to derive matched and unmatched samples. This will facilitate the planned statistical comparisons and modelling between the RCT and registry.

Brief Project Background and Statement of Project Significance:

RCTs and meta-analysis form the gold standard for determining the efficacy of treatments under optimal conditions but are often based on a restricted population: typically those patients at least risk of major adverse events. This limits generalisability. The short follow up of RCTs also hinders their ability to inform on attrition, treatment titration

and identification of rare, long-term adverse effects. These issues are of particular importance in the effective management of chronic conditions, such as inflammatory disease. Registries, on the other hand, demonstrate the effectiveness of a treatment under usual conditions, i.e. from a 'real-world' selection of patients many of whom would be excluded from RCTs due to more complex disease profiles. Hence registries can make a valuable contribution beyond RCTs, particularly in chronic conditions.

Several studies have been conducted to ascertain the contribution that registries offer to RCTs by comparing datasets. The methodology applied mainly consisted in the selection of registry patients based on the RCTs' eligibility criteria. The reported results are contradicting and inconclusive, so that investigating the development of novel methodology is valuable. Of note, differences between an RCT-eligible group and the actual recruited population are likely. Thus far, RCT and registry comparisons have been confined to the former; using the actual recruited RCT population may illustrate an even more restricted RCT population selection.
Rheumatoid arthritis (RA) is a common autoimmune disease. It is a chronic, systemic, inflammatory arthritis that leads to joint destruction and deformity with considerable personal, societal, and economic impact. RCTs have enabled the effective introduction of different conventional disease-modifying anti-rheumatic drug (DMARD) treatments and strategies into clinical practice, followed by the successful targeted biological DMARDs (bDMARDs). Only 15-35% of patients managed in the UK meet the strict eligibility criteria for RCTs, and clinicians struggle to achieve the same level of success when using bDMARDs in routine care. This is due to the heterogeneity of the RA population, the fact that most RCTs pre-date the treat to target approach (which emphasises tight control of disease activity to achieve remission) and national guidelines limiting use in the UK to severe disease. While bDMARDs are established in rheumatology practice following methotrexate failure, there is a need for additional guidance on the use of bDMARDs in RA to deliver cost-effective, yet highly effective care.
This project will identify patient profiles associated with wider effectiveness to bDMARDs by exploiting routine care observational data from a UK-based registry and comparing to RCTs. Methodologically, it will first establish whether SPD from published RCTs are appropriate to use in meta-analyses compared to IPD. The conditions of a RCT will be simulated within the registry population, which will provide evidence on the differences between efficacy in trials and effectiveness in clinical practice; this will inform clinicians how to extrapolate RCT results to real-world populations.

Specific Aims of the Project:

Hypotheses: 1) The heterogeneity of the real-world RA population leads to a heterogeneous treatment response, which differs from RCT results. 2) SPD, compared to IPD, is insufficient to inform about the individual factors that influence response to treatment.

This project aims to evaluate:
1. Differences in RA patient profiles and treatment outcomes between RCTs and registries.
2. Associations between patient characteristics and clinical response.
3. Differences between IPD and SPD when extrapolating RCT results to the registry population (explorative aim).

Objectives:
1. To compare and identify differences in patients' baseline characteristics of MTX-IR patients treated with infliximab as part of the ATTRACT RCT with those from the BSRBR-RA registry population to establish the degree of applicability of a RCT to the standard UK patient population.
2. To compare treatment outcomes between ATTRACT and the RCT-matched and unmatched registry sub-groups.
3. To establish which baseline characteristics from the registry are most strongly associated with improved outcomes.
4. To develop a method to select patients from the registry using SPD data from RCTs and compare the baseline characteristics and treatment outcomes with those selected using RCT IPD.

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 populationsNew research question to examine treatment safetyOther

Research Methods

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

RA will be used as a clinical demonstrator and infliximab as the selected therapy in the treatment of patients with

RA after conventional DMARD failure. Both Individual Patient-level Data (IPD) and Summary Patient Data (SPD) from the pivotal 'ATTRACT' trial [1] will be used to simulate a trial environment within the British Society for Rheumatology Rheumatoid Arthritis Register (BSRBR-RA). Only the patients randomised to receive infliximab as per current standard practice will be selected.

A data cleaning process has already been conducted to select those registry patients categorised as MTX-IR, were over 16 years of age at the time of registration, and had no overlapping or secondary autoimmune conditions that could affect safety outcomes. Patients enrolled in BSRBR-RA between October 2001 and May 2007 (first available cohort) and treated with infliximab will be eligible as they most closely reflect the time when the ATTRACT trial was undertaken.

The patient data from the control arm of the trial (treated with methotrexate and placebo) and the control group in BSRBR-RA will serve as a standard of comparison by which the effects of infliximab will be judged.

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

The main outcome measure is the difference in the proportion of patients with a 20 percent improvement in their clinical response (ACR20), according to the American College of Rheumatology (ACR), between the RCT ATTRACT patient population and the RCT-matched and unmatched sub-populations within the BSRBR-RA registry, at 12 months (54 weeks). To allow for the slight variation in the schedule of visits between the RCT and the registry, the 12-month visit is defined as the last visit on or before study week 54 (54 weeks = 12 months).

The ACR20 response is achieved by a relative improvement (reduction) from baseline of at least 20% in tender and swollen joint counts and a relative 20% improvement in 3 out of 5 following criteria [2]:

• Patient global health assessment of disease activity (measured by a Visual Analogue Scale (VAS))
• Physician global assessment of disease activity (measured by a VAS)
• Patient assessment of pain (measured by VAS)
• Patient assessment of physical function (measured by HAQ-DI questionnaire)
• Results of laboratory test for inflammatory marker (either erythrocyte sedimentation rate (ESR) or C-Reactive Protein (CRP))

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

The independent variable for this project is the administration of infliximab (Remicade, Centocor, Malvern, Pa.) in adult RA patients with active disease when the response to conventional disease-modifying anti-rheumatic drugs (cDMARDs), including methotrexate, has been inadequate (MTX-IR). The national guideline for the administration of infliximab is as described by the Summary of Product Characteristics (SPC); Infliximab should be administered at a dose of 3mg per kilogram of body weight per intravenous infusion at the initiation of treatment (week 0) and at weeks 2 and 6 and then at 8 weeks thereafter in combination with MTX. Standard-care registry patients are administered infliximab as prescribed by national guidelines, therefore only the data from ATTRACT patients randomised to receive 3 mg/kg infusion doses at 0, 2 and 6 weeks, then every 8 weeks thereafter will be used, together with the placebo arm, for the purposes of this project.

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

The following variables recorded at baseline will be compared between the RCT and the RCT-matched and -unmatched registry sub-populations, if available:
• Age at the time of presentation/baseline.
• Gender: percentage of females and males.
• Duration of disease: number of years since diagnosis of RA by a rheumatologist.
• Rheumatoid Factor (RF) – the percentage of patients with a positive result for RF will be compared.

The following variables will also be used in the analysis and the changes from baseline to months 6, 12, 24 and 36 (weeks 30, 54, 108 and 162) will be compared between the RCT and the registry sub-populations, if available:
• DAS28: disease activity score using 28 joint counts (tender and swollen)[3].
• EULAR response criteria[4]
• ACR50: calculated as the ACR20 (described above) but the relative improvement must be 50%.

• HAQ-DI©: Health Assessment Questionnaire Disability Index[5].
• SF36: The 36-Item Short Form Health Survey[6].
• Safety & Toxicity: co-morbidities secondary to RA recorded at baseline will be categorised by body system. Toxicity is defined as any symptom/event reported as an adverse event; these will be categorised by body system.

Statistical Analysis Plan:

Stata/SE version 12.1 for Mac StataCorp (College Station, TX, US) was used to perform descriptive summary statistics for all parametric and non-parametric registry data.
An anonymised extract of the BSRBR-RA dataset will be uploaded to the YODA's secure platform subject to permission being granted by BSR, in order to perform all the statistical analyses described here.
All future statistical analyses will be performed using R. A descriptive analysis will describe the baseline characteristics of all the registry sub-groups created.

The eligibility criteria from the RCT will be applied to BSRBR-RA to identify registry patients who fulfil the RCT criteria. Where a criterion stipulates a given range (e.g. laboratory measurements with a minimum and maximum reading) registry patients will be rated as meeting the criterion if their recorded result for the corresponding variable is within the given range. The identified registry patients (i.e. those who match the RCT's eligibility criteria) will be selected to form the 'RCT-eligible group'; those who do not fulfil the RCT's eligibility criteria will form the 'RCT-ineligible group'.

Only the baseline characteristics common to both the trial and the infliximab registry population will be used to match the two populations. A matching algorithm applicable for the IPD dataset from the ATTRACT RCT will be defined and applied to the RCT-eligible registry cohort. This will result in a subset of patients that 'match' the IPD dataset determined by the baseline characteristics of the actually recruited cohort from the ATTRACT RCT. This 'IPD-matched' population is therefore described as the registry sample representative of the randomized RCT sample. The remainder of patients from the infliximab registry cohort will constitute the 'IPD-unmatched' subset.

The SPD extracted from the ATTRACT publication will be used to develop a novel algorithm (based upon Markov Chain Monte Carlo methods) that will be applied to the RCT-eligible registry cohort, which will iterate until a sufficiently good fit between the registry sample and the SPD is found. Those registry patients who 'match' the summary baseline characteristics as per the ATTRACT publication will be described as the 'SPD-matched' subset. The remainder of patients will constitute the 'SPD-unmatched' subset.

Independent T test, Mann-Whitney U test, and Chi-squared tests will be applied to compare the baseline characteristics of patients in the different groups. The Wilson method will be used to calculate the 95% confidence intervals of proportions. All statistical tests applied will be two-sided. P values less than 0.05 will be considered statistically significant.
Wilcoxon signed rank tests, paired t-tests or McNemar's tests will analyse changes in treatment response over time. Multivariate linear regression models and Pearson/Spearman's correlation analyses will be used, as appropriate, to describe the associations between baseline characteristics and treatment outcomes. Similarly, safety outcomes (rate of adverse outcomes) will be considered using Poisson regression, classification trees and random forests.

Missing data will be explored by first tabulating missing data patterns. This will identify when specific groups of variables have missing values 'together', and quantify the extent of missing data. Multiple imputation methods are not relevant to this work, since it is unlikely that data are 'missing at random', which is an assumption necessary for multiple imputation to be valid. Single imputation has similar issues as well as reducing variability.

For key variables, the impact of missing data will be studied by sensitivity analyses. Specifically, missing values will be replaced by values determined to reveal the impact of the variable being considered. Each key variable will be considered consecutively. This is considered to be more informative than imputation methods which could be invalid.

Project Timeline:

The described project is part of a part-time PhD project, which commenced in October 2014. One third of the PhD project has been completed already. It is anticipated that the analysis completion date will be February 2018 with the subsequent drafting of the PhD thesis manuscript. The project is expected to be ready for submission by

October 2018. The project team is, however, aiming to be able to submit manuscripts for publication in peered reviewed scientific journals before and after the PhD thesis is submitted. The results from this project may, therefore, be reported back to the YODA Project as they become ready for being submitted for publication.

Dissemination Plan:

The results from this project will be of interest to a variety of audiences and therefore several journals will be considered for the submission of the different aspects of the project.

The benefit of the novel method developed as part of this project is two-fold: 1) It will provide methodologists/epidemiologists with a tool for maximising the clinical utility of existing registry data to assess the clinical effectiveness of therapies; methodology and epidemiology journals such as BMC Medical Research Methodology, Epidemiology, Journal of Clinical Epidemiology, and European Journal of Epidemiology will be considered. 2) It will provide rheumatologists with the means to identify patient characteristics that may be associated with certain biologic response outcomes; this will enable more appropriate and effective treatment decision-making in RA. Rheumatology-specific journals, such as Rheumatology or Annals of the Rheumatic Diseases, would be suitable for these outputs.

The results from the comparison on the use of IPD versus SPD would be of special interest to researchers conducting systematic reviews and meta-analyses in RA and other disease areas, therefore generic and RA-specific journals will be considered for submission of this output.

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Supplementary Material:


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