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Project Funding Source: National Institute of Health Research, UK

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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): NCT00265096 - A Multicenter, Randomized, Double-blind, Placebo controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously in Subjects with Active Psoriatic Arthritis
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Identifying the optimal target for Psoriatic Arthritis – a retrospective analysis to identify which target best predicts improved long term outcomes

Narrative Summary:
International Recommendations have suggested using a 'treat to target' approach in psoriatic arthritis (PsA) (1). The TIght COntrol of PsA (TICOPA) trial showed this can improve disease activity, function and quality of life (2). However there are several targets that could be used and the best has not yet been determined. PsA is a heterogeneous condition, with potentially important involvement across multiple domains of disease. We wish to use trial data to explore which targets are associated with the best long term outcome for patients in terms of x-ray damage to joints and functional ability. Then the best target can be implemented in practice, and lead to improved patient outcomes.

Scientific Abstract:
Background: Treating to target in PsA has been recommended internationally but multiple potential targets exist and the optimal target has not been identified.
Objective: To use retrospective analysis of data to examine 16 variations of 5 outcome measures that could serve as targets for therapy investigating which has the best prognostic value for long term function and structural damage outcomes in PsA.
Study design: Retrospective analysis comparing patients achieving different targets to establish which target has the best prognostic value for function and structural damage progression.
Participants: observed data from randomized patients with PsA in the GO-REVEAL trial with non-missing MDA and/or radiographic data at weeks 14, 24, 52, 104, 148, 196, and 256.
Main outcome measures: Change in function (health assessment questionnaire), structural damage, quality of life (SF-36) and productivity at week 256.
Statistical analysis: proportions achieving targets will be compared and residual disease activity quantified. Logistic regression will look for baseline predictors of achieving the targets and analyses of variance will compare the outcomes including radiographic damage, HAQ, SF-36 and patient global for participants achieving different targets either never, >2 and >3 timepoints (>38 and 90 weeks respectively).

Brief Project Background and Statement of Project Significance:
Treat to target recommendations for SpA, published in 2013 and drafted by expert consensus(3) stated that in PsA, the target of treatment should be remission or inactive disease. In some cases an alternative target of low or minimal disease activity was considered to be appropriate. At that time, no definitions of remission or inactive disease existed and the only validated target available was the minimal disease activity (MDA) criteria for PsA(4). The MDA criteria have been validated in numerous trial datasets(5-7) and were used in the only treat to target study in PsA to date(2). Since that time, other potential targets for both remission and low disease activity have been developed including cut offs for the Disease Activity in PsA (DAPSA) score(8, 9) (10). In addition, some proposals have been made with preliminary work on alternative versions of the MDA criteria(11). These include:
• addressing the requirement for either 6 or 7 of the 7 criteria to be met (rather than the original 5)
• MDA joints which requires that the two joint cut offs are met (tender and swollen joints ? 1) along with an

additional 3 of the 5 remaining measures
• MDA skin where the skin cut off is met, plus 4 of the remaining 6 measures
• MDA joints and skin where the joint and skin measures are met plus 2 of the remaining 4 measures.
It was also stated in these recommendations that a normalisation of a measure of systemic inflammation such as C-reactive protein should also be included in the definition of remission(12). CRP is not included in the MDA criteria and it is not clear what the addition of this requirement adds to the criteria, but this has not been explored.
Also since these recommendations were published, the first treat to target trial in PsA (the TICOPA study), using the MDA criteria as the target, has been presented and published(2). As we work towards translating the evidence based treat to target strategy into clinical practice, it would be ideal to recommend just one target for remission/inactive disease and low/minimal disease activity to ease education of physicians and feasibility in practice. However there is little data comparing these outcome measures and the potential consequences to patients of these targets.
Data from clinical trials in PsA are a unique source of information that is complete enough to allow calculation of the DAPSA scores, PASDAS, CPDAI, GRACE and the different MDA criteria. This will also allow us to evaluate the criteria in a subpopulation with active skin disease. By looking at the proportion of patients achieving these various criteria and their prognostic overall patient impact, we should be able to provide further evidence towards choosing optimal targets and optimizing patient outcomes.

Specific Aims of the Project:
The aim of this project is identify an evidence-based optimal treatment target for PsA that can be recommended for future trials and clinical practice.
The hypothesis is that differences between the definitions of remission, low and minimal disease activity will translate into differences in long term outcomes for patients. This will help us to identify an optimal target for therapy.
Our first objective is to examine compare different measures of remission or very low disease activity that may be appropriate for patients with a shorter duration of disease and less baseline joint damage so that these can be utilised in newly diagnosed patients. Our second objective is to compare different measures of minimal and low disease activity that may act as an alternative target in those with more established disease or pre-existing damage where remission may not be a realistic goal.

What is the purpose of the analysis being proposed? Please select all that apply. Other

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
These post-hoc analyses of the GO-REVEAL trial will utilize observed data from randomized patients with non-missing MDA and/or radiographic data at weeks 14, 24, 52, 104, 148, 196, and 256, time points at which data were available to analyze the MDA status.

Main Outcome Measure and how it will be categorized/defined for your study:
The main outcome will be change in health assessment questionnaires (HAQ) at week 256. This will be defined as change in score from baseline to week 256 and will be used as our key long term outcome in this study.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The MDA includes : tender joint count (TJC) ?1; swollen joint count (SJC) ?1; Psoriasis Activity and Severity Index (PASI) ?1; patient pain visual analogue score (VAS) ?15 mm; patient global disease activity VAS ?20 mm; health assessment questionnaire score ?0.5; and ?1 tender entheseal points.
Six variations of MDA will be tested. Achieving at least 5, 6 or all 7 of the 7 variables. Also definitions requiring 5 variables but with either or both peripheral arthritis and skin activity mandated.
The disease activity in PsA (DAPSA) score = TJC + SJC + Pt VAS (cm) + Pt pain (cm) +CRP (mg/dl). The clinical DAPSA = TJC + SJC + Pt VAS (cm) + Pt pain (cm). Remission is ?4 for both and low disease activity is ?14 and 13 respectively.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
The PsA disease activity score (PASDAS) score is calculated as 0.18 x ?physician global VAS + 0.159 x ?patient global VAS - 0.253 x ?Short form 36 physical component score (SF36-PCS) + 0.101 x ln (SJC+1) + 0.048 x ln

(TJC+1) + 0.23 x ln (Leeds enthesitis index (LEI) +1) + 0.37 x ln (tender dactylitis count+1) + 0.102 x ln (C reactive protein (CRP)+1). Low and very low disease activity are 3.2 and 1.9.
The GRAPPA Composite index (GRACE) score is calculated using desirability functions. Low disease activity is <2.3. The Composite PsA disease activity index (CPDAI) is calculated on a grid where domains are scored 0-3 according to their disease activity and impact. Definitions for low disease activity and very low disease activity are 4 and 2 respectively.

Statistical Analysis Plan:
The following targets will be tested
1. MDA 5 of 7 variables
2. MDA 6 of 7 variables
3. MDA 7 of 7 variables
4. MDA joints
5. MDA skin
6. MDA joints and skin
7. DAPSA remission
8. cDAPSA remission
9. DAPSA low disease activity
10. cDAPSA low disease activity
11. PASDAS low disease activity
12. PASDAS very low disease activity
13. CPDAI low disease activity
14. CPDAI very low disease activity
15. GRACE low disease activity
16. GRACE very low disease activity

Proportions achieving the targets will be compared at a group and individual level. For those meeting the targets, residual disease activity will be quantified using descriptive analysis including values of systemic inflammatory response.
The endpoints at >2 and >3 consecutive time points (>38 and 90 weeks), based on a previous publication(7), provide a reasonable number of patients for analysis in a clinically meaningful and sustained timeframe.

Logistic regression analyses will assess the effect of baseline characteristics on achievement of the targets, including HAQ DI score, MTX use, patient global, PsA duration, joint counts, and CRP level.

Analyses of variance will compare outcomes of interest including changes from baseline to week 256 in the PsA-modified Sharp/van der Heijde score (SHS), HAQ DI score, SF-36, productivity score, PASI score, and patient global for different target categories including: never; >2 and >3 consecutive time points.

Project Timeline:
Application submitted to YODA August 2016
Approval from YODA September 2016
Project start date (receipt of data) 1st October 2016
Analysis completion date 31st December 2016
Draft manuscript completed and submitted for publication 1st April 2017
Results reported to YODA 1st April 2017

Dissemination Plan:
The dissemination will be via two main outputs. Firstly we anticipate an original research paper reporting the findings that would also be submitted in abstract form. Given the timelines above, we plan to submit an abstract summarising the data to the European League Against Rheumatology (EULAR) for their deadline for submissions of 31st January 2017. We believe that the manuscript would be of high interest to those in the field of PsA and would plan to submit for publication in the Annals of the Rheumatic Diseases or Arthritis Care and Research. Secondly, this data will inform an ongoing project within the Group for Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) to form an expert international consensus on the optimal target for treatment in PsA. This data will contribute to the ongoing project (with data from other studies) and this will form the basis of an expert consensus meeting where opinions of rheumatologists, dermatologists and patient research partners will be sought with an aim of producing a recommendation paper supporting translation of this trial evidence into routine clinical practice.

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