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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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_da_signed.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors-ak.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors-js2.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

1. NCT00299546 - C0524T11 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously in Subjects with Active Rheumatoid Arthritis and Previously Treated with Biologic Anti TNFa Agent(s)
2. NCT01606761 - CNTO136ARA3003 - A Multicenter, Randomized, Double-blind, Placebo-controlled,

Parallel Group Study of CNTO 136 (Sirukumab), a Human Anti-IL-6 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Rheumatoid Arthritis Despite Anti-TNF-Alpha Therapy

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 factors related to high placebo response rates in patients with active rheumatoid arthritis despite prior treatment with biological agents

Narrative Summary:

Trials investigating biological disease modifying anti-rheumatic drugs (bDMARDs) in rheumatoid arthritis have caused some concerns regarding the patient populations included, as in many trials placebo (PLC) response rates were observed to be unexpectantly high. Many patients included in these trials received concomitant conventional synthetic (cs)DMARDs. Two recent studies did, nevertheless, additionally include patients receiving PLC treatment only. In this project we therefore want to investigate, if the high observed PLC response rates might be due to the concomitant csDMARD therapy by comparing results in those receiving csDMARDs in addition to placebo with placebo-only treated patients.

Scientific Abstract:

Background
High placebo (PLC) response rates in rheumatoid arthritis (RA) trials investigating patients with insufficient response (IR) to biological disease modifying antirheumatic drugs (bDMARDs) were reported. Patients randomized to PLC arms in previous trials most commonly included patients receiving concomitant conventional synthetic (cs)DMARDs. The GO-AFTER and the SIRROUND-T studies, however also included patients receiving PLC treatment only as well patients with csDMARD therapy and therefore provide the possibility to investigate PLC arm responses.(1,2)
Objective
To compare the effect of csDMARD treatment in PLC arms with PLC only treated patients in two trials investigating RA patients with bDMARD-IR.
Study design
Retrospective analysis of two randomized controlled double-blind trials.
Participants
Patients included in the GO-AFTER and SIRROUND-T studies randomized to the PLC arms.
Main Outcome Measures
Main outcomes are the ACR20/50/70 responses at the primary endpoints (wk 14/16).(3) Secondary analyses include individual core set components, the clinical and simplified disease activity index (CDAI/SDAI), physical function and structural damage.(4)
Statistical analysis
Cochran-Mantel-Haenszel tests shall be used to compare ACR20/50/70, CDAI and SDAI REM/LDA responses in patients receiving concomitant csDMARDs to patients receiving PLC treatment only. Physical function and radiographic progression will be compared using ANCOVA. Longitudinal analysis of CDAI, SDAI, ACR core set parameters and physical function will be analysed using mixed model analysis

Brief Project Background and Statement of Project Significance:

Many new therapies have evolved over the past decades for patients suffering from rheumatoid arthritis. Therapies targeting, and inhibiting tumor-necrosis-factor alpha and other molecules involved in the inflammatory pathway (e.g. interleukin 6) have shown to be effective in RA patients with insufficient response to conventional and biological therapies. Interestingly, placebo response rates were observed to be unexpectantly high in many studies, even in patients who were bDMARD insufficient responders (IR). Nevertheless, in most studies investigating bDMARDs-

IRs, patients in the placebo group received concomitant csDMARD therapy. Therefore, patients' placebo response could possibly be explained by an actual response to the concomitant csDMARD therapy because of better adherence to therapy while being included into the study. Until now, according to the applicants' knowledge only two studies (the GO-AFTER and the SIRROUND-T study) included patients in the placebo arms who received placebo treatment only next to patients with csDMARD background therapy. Thus, these two studies allow the direct comparison of patients included in the placebo group, enabling us to potentially identify csDMARD use as the reason for high placebo-group response rates. Furthermore, specific investigation of ACR core-set variables, radiographic progression and patient demographics may additionally allow to identify other important response determinants in those two separate subgroups of placebo patients. The results of this study would provide essential information for investigators, methodologists, sponsors and regulatory agencies, but also clinical rheumatologists of how to interpret placebo responses and furthermore, how to define the target population in future RA trials.

Specific Aims of the Project:

The aim of this project is to identify factors responsible for high placebo rates in RA randomized controlled studies investigating patients with insufficient response to bDMARDs. The main hypothesis is that patients included in placebo arms respond to csDMARD background therapy after being included in the study, leading to higher response rates. The GO-AFTER and SIRROUND-T study investigated bDMARD-IR patients, but included patients with and without csDMARD background therapy. We propose to investigate, if those placebo subgroups show differences in achieving ACR responses (20/50/70) and other important outcomes, such as states of low disease activity by SDAI/CDAI, physical function and radiographic progression.

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 populations

Research Methods

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

All patients randomized to the placebo group of the GO-AFTER and the SIRROUND-T study.

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

The difference of the American College of Rheumatology (ACR) 20 response between patients receiving placebo treatment only compared to patients receiving csDMARD background therapy is the main outcome measure of this study. The definition of the ACR response was developed in 1995 by Felson et al. (3)

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

The categorization of patients depends on receiving csDMARD background therapy (yes/no) additionally to placebo treatment during the study. Receiving background csDMARD therapy vs. placebo treatment only is therefore considered as the predictor variable.

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

Other variables of interest are patient demographics (age, sex, disease duration, previously received therapies, ethnicity, country of study center) as well as all ACR core-set-variables (Swollen joint count 66 (SJC66), tender joint count 68 (TJC68), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), pain, evaluator global assessment of disease activity (EGA), patient global assessment of disease activity (PGA), physical function as measured by the Health Assessment Questionnaire Disability Index (HAQ) or the Short-Form 36 Physical Component Score (SF36-PCS)) to identify differences in responses of the described patient subgroups. Further differences in radiographic progression (as measured by the Sharp-van-der-Heijde Score) are to be compared between the subgroups.

Statistical Analysis Plan:

The two groups for comparison are patients receiving csDMARD background therapy additionally to placebo treatment (PLCDMARD) and patients receiving placebo treatment only (PLCONLY).
Primary outcome measure: Cochran-Mantel-Haenszel test to compare ACR20 response rates (GO-AFTER: week 14; SIRROUND-T: week 16) between PLCDMARD and PLCONLY patients.
Secondary outcome measures:
Comparison of ACR50 responders (Cochran-Mantel-Haenszel test) between PLCDMARD and PLCONLY.
Comparison of AC750 responders (Cochran-Mantel-Haenszel test) between PLCDMARD and PLCONLY.
Comparison of patients in CDAI remission (<2.8) (Cochran-Mantel-Haenszel test) between PLCDMARD and PLCONLY.
Comparison of patients in CDAI low disease activity (<10) (Cochran-Mantel-Haenszel test) between PLCDMARD and PLCONLY.
Determination of differences (between PLCONLY and PLCDMARD) in change from baseline of ACR core set variables (SJC66, TJC68, PGA, EGA, CRP, ESR, HAQ, SF36-PCS), change in CDAI and SDAI, as well as Sharp-van-der-Heijde score using linear mixed models (respective change from baseline as independent variable; group and baseline value of corresponding variable and interaction term as dependent variables; all available visits from baseline to the primary efficacy endpoint (week 14/16) are included as repeated measurements by patient; the Variance-Covariance matrix will be selected according to the best (lowest) fit criteria).
Determination of the influence of demographics (age, sex, disease duration, trial center, ethnicity) on achieving of ACR 20/50/70 responses using logistic mixed models (Independent variable: ACR20/50/70 response at week 14/16 (yes/no); dependent variable: respective demographic variable).
All analyses will be conducted using STATA.

Project Timeline:

Project start date: January 2nd, 2019
Data preparation: January - February 2019
Analysis of data: February – March 2019
Writing of scientific article + Submission: April 2019 – October 2019

Dissemination Plan:

The results of this study will be presented at major international conferences, such as EULAR and ACR, but also national meetings. It is planned to write a scientific paper on the results. Potentially suitable journals for submission are the Annals of Rheumatic Diseases, Arthritis and Rheumatology and Rheumatology (Oxford).

Bibliography:

1. Aletaha D, Bingham CO, Tanaka Y, Agarwal P, Kurrasch R, Tak PP, et al. Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): a randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3 study. The Lancet. 2017 Mar 25;389(10075):1206–1217.
2. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. The Lancet. 2009 Jul 18;374(9685):210–221.
3. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995 Jun;38(6):727–735.
4. Aletaha D, Nell VPK, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005 Apr 7;7(4):R796–806.