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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

http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_kaoru.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_diane_0.pdf
http://yoda.yale.edu/system/files/coi_yoda_sofia_ramiro.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. NCT00299546 - 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
2. NCT00236028 - A Randomized, Double-blind, Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab)

in Combination With Methotrexate Compared With Methotrexate Alone for the Treatment of Patients With Early Rheumatoid Arthritis
3. NCT00732875 - A Placebo-controlled, Double-blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody (cA2) in Korean Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment (Open-label Extension Part)

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

Research Proposal

Project Title

Effect of rheumatoid factor and anticitrullinated peptide antibody on the efficacy of bDMARDs in patients with RA

Narrative Summary:

The purpose of this study is to investigate the role of autoantibodies in the response of RA patients to biological disease-modifying antirheumatic drugs (bDMARDs). More specifically we aim at understanding whether there is a different efficacy of bDMARDs in seropositive patients compared to seronegative patients. Addressing this issue may aid healthcare providers to make better treatment decisions for RA patients. This study question arose in the context of the EULAR taskforce for the management of RA, and it is undertaken under the auspices of that taskforce.

Scientific Abstract:

Background; Although bDMARDs have significantly improved clinical outcomes of RA patients, the association between the presence of autoantibodies and efficacy of bDMARDs has not yet been thoroughly studied.
Objective; The purpose of this study is to investigate the role of autoantibodies in the response to bDMARDs. More specifically we aim at understanding whether there is a different efficacy of bDMARDs in seropositive patients compared to seronegative patients.
Study Design; We are conducting a systematic literature review, if possible complemented by a meta-analysis. RCTs have been identified through previous SLRs addressing the efficacy of bDMARDs to inform the EULAR recommendations for the management of RA.
Participants; Studies that included both autoantibody-positive and negative patients (with the percentage of seropositive patients being ?80%) fulfilling the 1987 or 2010 RA criteria will be eligible. Interventions considered will be on-label dose of bDMARDs and any comparator. Strategy trials will not be included.
Main Outcome Measures; The primary endpoint is the ACR20 response at 6 months. Secondary endpoints are the change in DAS28-ESR, ACR50 response, ACR70 response, achievement of remission, change in HAQ, and progression in total Sharp score, at 6 months. All endpoints will be analyzed in subgroups of patients according to baseline auto-antibody status.
Statistical Analysis; The first step is to collect the above-mentioned endpoints stratified for baseline auto-antibody status. Having all data, we will conduct a meta-analysis of RCTs.

Brief Project Background and Statement of Project Significance:

The purpose of this study is to investigate the role of autoantibodies in the response of RA patients to bDMARDs. More specifically we aim at understanding whether there is a different efficacy of bDMARDs in seropositive patients compared to seronegative patients. Addressing this issue may aid healthcare providers to make better treatment decisions for RA patients. This study question arose in the context of the EULAR taskforce for the management of RA, and it is undertaken under the auspices of that taskforce.
We are conducting a systematic literature review to address this unmet need. In our search, we found three publication concerning the following trials: ASPIRE trial (Arthritis Rheum. 2004 Nov;50(11):3432-43), GO-AFTER trial (Lancet. 2009 Jul 18;374(9685):210-21), and published by Kim et al (J Korean Med Sci. 2013 Dec;28(12):1716-22). The results of the trial are very interesting to us. Unfortunately the publication did not contain exact data about the number of autoantibody-positive and –negative patients and about the treatment response for

patient subgroups with and without autoantibodies. We are interested in the rheumatoid factor- and ACPA-status of the participants at baseline. We are then primarily interested in disease activity measures at the trial's endpoints for these different subgroups.

Specific Aims of the Project:

Although bDMARDs have significantly improved clinical outcomes of rheumatoid arthritis (RA) patients, better predictors of treatment response in individual patients are still needed. Patients who are positive for the anticitrullinated peptide antibody (ACPA) are known for having worse clinical and radiographic outcomes, compared to ACPA-negative patients. Previous studies have suggested that the presence of autoantibodies is associated with a higher efficacy of bDMARDs when compared to seronegative patients. However, this phenomenon has not yet been thoroughly studied. The purpose of this study is therefore to investigate the role of autoantibodies in the response to bDMARDs. More specifically we aim at understanding whether there is a different efficacy of bDMARDs in seropositive patients compared to seronegative patients. Addressing this issue may aid healthcare providers to make better treatment decisions and ultimately improve the care for RA patients.

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 populationsSummary-level data meta-analysisSummary-level data meta-analysis pooling data from YODA Project with other additional data sourcesOther

Research Methods

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

We are conducting a systematic literature review. RCTs have been identified through previous SLRs addressing the efficacy of bDMARDs to inform the EULAR recommendations for the management of RA [1-3].
Studies that included both autoantibody-positive and negative patients (with a percentage of seropositive patients ?80%) fulfilling the 1987 or 2010 RA criteria will be eligible. Interventions considered will be on-label dose of bDMARDs and any comparator. Strategy trials will not be included, as due to their complex design they do not allow to properly investigate the effect of bDMARDs in subgroups of patients (seropositive vs seronegative) without the confounding effect of the steered-treatment.

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

Primary Endpoint: ACR20 response at 6 months.
Secondary Endpoints: The change in DAS28-ESR, ACR50 response, ACR70 response, achievement of remission, change in HAQ, and progression in total Sharp (van der Heijde) score, all at 6 months.
The same outcomes at 12 and at 24 months, but not compared to placebo as there is no placebo-controlled arm beyond 6 months, but only to analyze whether there is a sustainability of response.
All endpoints will be analyzed in subgroups of patients according to baseline auto-antibody status.

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

Main predictor/independent variable is baseline auto-antibody status. Subgroup analyses based on the following subgroups will be performed for all endpoints: 1) ACPA-negative and RF-negative, 2) ACPA-negative and RF-positive, 3) ACPA-positive and RF-negative, 4) ACPA-positive and RF-positive.

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

None

Statistical Analysis Plan:

The first step is to collect the endpoints on disease activity, function and radiographic progression, stratified for baseline auto-antibody status. Subgroup analyses based on the following subgroups will be performed: 1) ACPA-negative and RF-negative, 2) ACPA-negative and RF-positive, 3) ACPA-positive and RF-negative, 4) ACPA-positive and RF-positive. A standardized data extraction sheet is provided for the collection of these data.

The Cochrane risk of bias assessment tool will be used to assess the risk of bias of each of the studies. For every individual study, the following analysis methods will be used for the primary and secondary outcomes: The risk ratio (RR) and 95% confidence intervals (CI) of ACR20, ACR50, ACR70 response, and achievement of remission will be calculated using the Mantel-Haenszel method. The change from baseline in DAS28-ESR, HAQ, and total Sharp score will be calculated by standardized mean differences using the generic inverse variance method. All the primary and secondary outcomes will be compared between the seropositive and seronegative patients. Heterogeneity will be indicated by I2 wherein 0% means no heterogeneity and 100% means the strongest heterogeneity. Estimates will be pooled according to the random effects model.

Project Timeline:

Project start date: 10/01/2017
Analysis completion date: 10/01/2018
Date manuscript drafted and first submitted for publication: 06/01/2019
Date results reported back to the YODA Project: 06/01/2019

Dissemination Plan:

Results of this project will be presented at main international conferences in Rheumatology, namely EULAR and ACR. The plan is to present them in 2018 (provided data from all/most eligible RCTs could have been gathered; otherwise in 2019). A manuscript will be submitted to a high impact factor journal in the area of rheumatology.

Bibliography:

1. Nam JL, Takase-Minegishi K, Ramiro S, Chatzidionysiou K, Smolen JS, van der Heijde D, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2017 Jun;76(6):1113-1136.
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3. Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis. 2010 Jun; 69(6):976-986.
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5. Kim J, Ryu H, Yoo DH, Park SH, Song GG, Park W, Cho CS, Song YW. A clinical trial and extension study of infliximab in Korean patients with active rheumatoid arthritis despite methotrexate treatment. J Korean Med Sci. 2013 Dec;28(12):1716-22.
6. 4. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, Gaylis N, Murphy FT, Neal JS, Zhou Y, Visvanathan S, Hsia EC, Rahman MU; GO-AFTER study investigators. 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. Lancet. 2009 Jul 18;374(9685):210-21.

Supplementary Material:

20171217_yoda_project_yoda_aspire_final_clear_version.docx yoda_project_kim_2013.docx

yoda_project_go-after.docx 20171217_response_to_reviewer_final.docx