Principal Investigator

First Name: Johanna
Last Name: Gehin
Degree: MD, PhD
Primary Affiliation: Oslo University Hospital
E-mail: johgeh@ous-hf.no
State or Province: Oslo
Country: Norway

General Information

Key Personnel (other than PI):
First Name: Joseph
Last name: Sexton
Degree: PhD
Primary Affiliation: Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway
SCOPUS ID:
Requires Data Access? Yes

First Name: Silje Watterdal
Last name: Syversen
Degree: PhD
Primary Affiliation: Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway
SCOPUS ID:
Requires Data Access? No

First Name: Nils
Last name: Bolstad
Degree: PhD
Primary Affiliation: Department of Medical Biochemistry, Oslo University Hospital, Oslo Norway
SCOPUS ID:
Requires Data Access? No

First Name: Guro Løvik
Last name: Goll
Degree: PhD
Primary Affiliation: Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway
SCOPUS ID:
Requires Data Access? No

First Name: Ingrid
Last name: Jyssum
Degree: MD
Primary Affiliation: Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway
SCOPUS ID:
Requires Data Access? Yes

First Name: Eirik Klami
Last name: Kristianslund

Degree: PhD
Primary Affiliation: Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway
SCOPUS ID:
Requires Data Access? No

First Name: Espen
Last name: Haavardsholm
Degree: Professor, PhD
Primary Affiliation: Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway
SCOPUS ID:
Requires Data Access? No

First Name: Rolf Anton
Last name: Klaasen
Degree: PhD, MS
Primary Affiliation: Department of Medical Biochemistry, Oslo University Hospital
SCOPUS ID:
Requires Data Access? Yes

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: EU (Horizon 2020)
How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2023/09/COI-form_Syversen-SW.pdf
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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

1. NCT00207714 - C0524T02 - A Randomized, Double-blind, Dose-ranging Trial of CNTO 148 Subcutaneous Injection Compared With Placebo in Subjects With Active Rheumatoid Arthritis Despite Treatment With Methotrexate
2. NCT00264550 - C0524T06 - 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 Despite Methotrexate Therapy
3. NCT00264537 - C0524T05 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered

Subcutaneously, in Methotrexate-naïve Subjects with Active Rheumatoid 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

Personalized dosing of golimumab based on serum drug concentrations in patients with rheumatoid arthritis

Narrative Summary:

Rheumatoid arthritis (RA) constitutes a significant burden for patients and society. Tumor necrosis factor inhibitors (TNFi) are effective treatments, but some patients fail to respond. Strategies to maximize efficacy of TNFi, including golimumab, are thus needed. Therapeutic drug monitoring (TDM) may optimize efficacy and cost-effectiveness of treatment with TNFi, as demonstrated for infliximab in the NOR-DRUM B trial. More knowledge is needed regarding the clinical utility of TDM of subcutaneous TNFi. This requires identifying the therapeutic ranges, i.e the optimal serum drug concentration for effect. The main aim of the current project is to identify the therapeutic range for golimumab.

Scientific Abstract:

Background: Tumor necrosis factor inhibitors (TNFi), including golimumab, have greatly improved treatment of rheumatoid arthritis, but some patients fail to respond to these treatments or lose response over time. Therapeutic drug monitoring (TDM), i.e concentration-based dosing, may optimize efficacy and cost-effectiveness of treatment with TNFi. In order to validate TDM as a clinical tool, therapeutic ranges, i.e the optimal serum concentration which is both effective and safe, must be identified.
Objective: To identify the therapeutic range for golimumab.
Study design: The proposed project will apply already available data from phase III studies of golimumab to study the relationship between serum golimumab concentration and clinical effect, in order to identify the therapeutic range.
Participants: Rheumatoid arthritis patients in the treatment arms starting golimumab in phase III trials; NCT00207714, NCT00264550, NCT00264537.
Primary and Secondary Outcome Measure(s): European Alliance of Associations for Rheumatology (EULAR) good/moderate response, change in Disease Activity Score 28 joints (DAS28) score, DAS28 improvement ≥0.6/1.2 from baseline, DAS28 remission (score <2.6) or low disease activity (score 2.6-3.2), tender joint count, swollen joint count, change in C-reactive protein (CRP), American College of Rheumatology (ACR) 70, 50, 20 responses (70, 50, 20 % improvement from baseline).
Statistical analysis: Exploratory analyses of the association between serum drug levels and disease activity, including both graphical and regression based techniques.

Brief Project Background and Statement of Project Significance:

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease characterized by symmetric inflammation of the peripheral joints [1]. RA constitutes a significant burden for the individual patient and incurs substantial direct and indirect costs on society [2]. Tumor necrosis factor inhibitors (TNFi), including golimumab, have revolutionized the treatment of RA, but not all patients respond adequately [3, 4]. Strategies to maximize treatment efficacy of TNFi treatment are thus needed. Therapeutic drug monitoring (TDM), refers to measurements of blood concentrations to guide individual dose adjustments, which may optimize efficacy and cost-effectiveness of treatment

with TNFi [5, 6]. Methods for assessment of serum drug concentrations are available for use in clinical practice. Observational studies have shown associations between serum drug levels and effectiveness and also revealed considerable inter-individual variation in serum drug levels for TNFi, including golimumab, indicating both under- and overexposure [7-9]. Development of anti-drug antibodies (ADAb) is a major reason for low drug levels and lack of effectiveness of TNFi [6].

TDM of TNFi is a topic of great interest among clinicians treating patients with immune-mediated inflammatory diseases, including rheumatologists and gastroenterologists. The interest in TDM has been further spiked by the two randomized clinical Norwegian Drug Monitoring (NOR-DRUM) trials, conducted by our research group, both published in JAMA [10, 11]. NOR-DRUM B demonstrated that TDM leads to better outcomes in the maintenance phase of treatment with the TNFi infliximab across patients with immune-mediated inflammatory diseases. However, more knowledge is needed regarding the clinical utility of TDM of subcutaneous TNFi [12].

The SQUEEZE project is a European research consortium investigating personalized medicine for RA. The project is funded by EU (Horizon 2020), headed by Daniel Aletaha, Medical University of Vienna. https://squeeze-project.eu/. Work package 6 of the SQUEEZE project entails maximizing benefit of biologic disease-modifying antirheumatic drugs, such as TNFi, by TDM. To validate the use of TDM, therapeutic ranges, i.e the optimal serum drug concentration for effect, must first be identified. For golimumab, the therapeutic range remains unclear and current data is based on small observational studies [9, 13].
Data from dose finding studies and phase III trials represent a unique opportunity to identify the therapeutic range as well as the effect of dose adjustments on serum drug concentrations. By facilitating personalized treatment with TNFi, the proposed research has potential to improve treatment and quality of life for a large group of patients with RA.

Our project group has a solid track record in TDM research, including assessment of observational data to develop therapeutic ranges, as well as conducting clinical trials, and participation in international expert groups on TDM of biologic drugs. Our group thus has the necessary competence and resources to further develop this field.

Specific Aims of the Project:

Primary aim: To identify the therapeutic range for golimumab.
Secondary aims:
• To assess the influence of age, gender, body-weight/BMI, smoking habits, disease activity, concomitant methotrexate and anti-drug antibodies (ADAb) on serum levels and effectiveness of golimumab.

• To assess the effect of different doses and dose adjustments on serum levels of golimumab.

Hypotheses:
• There exists a concentration-effect relationship for golimumab and a therapeutic range can be identified
• Patients, disease and treatment characteristics influence the relationship between serum golimumab concentration and effect
• Serum drug levels are dependent on dose in a predictable manner

Study Design:

Other

Study Design Explanation:

Individual trial analyses. In addition, data on serum golimumab concentration and outcome measures from the three trials (NCT00207714, NCT00264550, NCT00264537) may be pooled if deemed appropriate.

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

Other: Identify the therapeutic range for golimumab, to be incorporated in treatment algorithms in future clinical trial examining the clinical utility of concentration-based dosing (i.e TDM) of golimumab in rheumatoid arthritis.

Research Methods

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

Inclusion: All patients randomized to receive golimumab and with available serum golimumab concentration measurement in the three studies. Data from the entire Intent-to-treat population is desirable, as inclusion of patients with lack of effect, non-compliance and adverse events, etc. are necessary to study the effect of serum levels on clinical effect.
Exclusion criteria: Patients who did not receive the allocated treatment. Patients with missing serum golimumab concentration or outcome data at ≥2 time points of interest.
Time points of interest:
NCT00264550 and NCT00264537: Baseline, W12 and W 24.
NCT00207714: Baseline, W12 and W 24, Time of interval prolongation (W20), W36 and W48.

The requested data are applicable to meet our aims;
1. All three studies include data on serum golimumab concentration, relevant covariates (age, gender, body-weight/BMI, smoking habits, disease activity, concomitant methotrexate and anti-drug antibodies), and clinical and biochemical outcome measures. These data will be used to assess the relationship between serum golimumab concentration and clinical effect, in order to identify the concentration-effect curve and hopefully the therapeutic range.
2. In all three studies, patients received golimumab 50 or 100 mg monthly. The data are thus applicable to study the relationship of two different doses and serum concentration. Data from NCT00207714 are also applicable to assess the effect of interval prolongation from 2 to 4 weeks.
3. Phase III trials includes data from more patients than what is usually feasible in a cohort and we consider it an advantage to use data from the phase III trial due to high validity.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary outcome measures:
-European Alliance of Associations for Rheumatology (EULAR) response; no response (change in DAS28 ≤0.6), moderate response (current DAS28 <5.1 and change in DAS28 >1.2, or current DAS28 ≤5.1 and >3.2, and change in DAS28 >0.6, or current DAS28 ≤3.2 and change in DAS28 >0.6 and ≤1.2), good response (current DAS28 ≤3.2 and change in DAS28 >1.2)),
-Disease activity score 28 joints (DAS28) improvement from baseline (continuous variable).

Secondary outcome measures:
-DAS28 disease state (remission <2.6, low disease activity 2.6-3.2, moderate disease activity >3.2-5.1 and high disease activity >5.1)
-Change in number of tender joints (0-68) (continuous variable)
-Change in number of swollen joints (0-66) (continuous variable),
-Change in C-reactive protein (CRP) level (mg/dL) from baseline (continuous variable)
-American College of Rheumatology (ACR) 70, 50, 20 responses (70, 50, 20 % improvement from baseline).
-Number of adverse events (including infections) (yes/no, might be classified according to MedDRa if applicable) (continuous variable).
-Treatment discontinuation due to lack of efficacy, adverse event or other reason, yes/no, number of

patients.

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

Serum golimumab concentration. The variable will be assessed as a continuous variable and in categories/quantiles e.g in deciles.

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

Age, sex, race, weight, BMI, RF and ACPA-status and level IU/ml, symptom duration before diagnosis, disease duration/diagnosis date, prior biologic DMARD use, smoking (no, previous, current).
Golimumab dosages.
Co-treatment methotrexate and corticosteroids; dose.
Anti-drug antibodies.

Statistical Analysis Plan:

The determination of a therapeutic range for golimumab serum levels will be done through a combination of receiver-operating characteristic curve analyses, explorative, and regression analysis-based techniques. The explorative analysis will, e.g., involve segmenting the range of serum levels and summarizing corresponding disease activity assessments made at the same time points. Appropriate regression analysis techniques, depending on outcome characteristics and including possibly non-parametric variants, will be used to assess and estimate the association between serum levels and disease activity. Multivariable analyses will be carried out to adjust for potential confounders (incl. age, gender, disease duration and prior use of bDMARD (Yes/No), concomitant methotrexate and body mass index).

Assessment of how golimumab serum levels respond to changes in golimumab dosage (NCT00207714): Explorative data analysis techniques will initially be used. These will include, e.g., scatter plots of golimumab serum levels pre and post dosage changes (stratified by change magnitude), both on the original scale and of transformations (e.g. logarithmic), and scatter-(box-) plots of relative dosage change and corresponding serum level change.

Associations between baseline variables and golimumab serum concentration will be assessed using descriptive statistics, including independent sample T-test, Mann-Whitney U tests for continuous variables or Chi-Square test for cathegorical variables.
Handling of missing data: Handling of missing data will depend on the extent of the problem. The analysis might use complete case or simple imputation techniques if the extent of missingness is minor, but multiple imputation will be employed if this is deemed not to be the case. If multiple imputation is employed, composite disease activity scores will be imputed by first imputing their component scores. Imputation models will be formed using all available observations, with the particular model type (e.g. multivariate normal model or chained equations (MICE)) determined through explorative analysis. If two substantively different models are suggested both will be implemented to assess robustness.

Effect measures: Mean/median change
Odds ratio (95% CI)
Regression coefficient (β), Correlation coefficient (R)

Methods to control for bias: multivariable analyses adjusting for covariates.

Strategy to maintain independence of the datasets/account for differences in study populations: Data from different studies will initially be analyzed separately.
If deemed appropriate, however, pooled analyses will be considered. The studies include the same outcome measures. If pooled analyses is deemed appropriate, statistical adjustments for differences

in available population characteristics will be made. Study level indicators will also be included in pooled analyses, and their interaction with relevant predictors will be considered.

Software Used:

STATA

Project Timeline:

December 2023; Estimated start of data processing.
January 2024; Estimated start of data analyses.
December 2024; Estimated publication of results.

Dissemination Plan:

The results will be published in a peer-reviewed scientific journal with rheumatologists as target audience.
The therapeutic range identified in this study will be incorporated into future clinical trials assessing the effectiveness of TDM of TNFi such as golimumab for rheumatoid arthritis patients.

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