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Requires Data Access? Yes

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?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/04/COI-Lihi-Eder.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/COI-RC.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/COI-LZ.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/COI-MY.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. NCT00265096 - C0524T08 - 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
2. NCT02181673 - CNTO148PSA3001 - A Study of Golimumab in Participants With Active Psoriatic Arthritis
3. NCT01009086 - CNTO1275PSA3001 /// PSUMMIT I - A Study of the Safety and Effectiveness of Ustekinumab in Patients With Psoriatic Arthritis
4. NCT01077362 - CNTO1275PSA3002 /// PSUMMIT II - A Study of the Safety and Efficacy of Ustekinumab in Patients With Psoriatic Arthritis With and Without Prior Exposure to Anti-TNF Agents
5. NCT00267956 - C0743T10 - A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of CNTO 1275, a Fully Human Anti-IL-12 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Psoriatic Arthritis
6. NCT00051623 - C0168T50 - A Multicenter, Randomized, Double-blind Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab) for the Treatment of Patients With Psoriatic Arthritis
7. NCT00367237 - P04422 - A Randomized, Multicenter, International, Open-label Study of Infliximab Plus Methotrexate Versus Methotrexate (MTX) Alone for the Treatment of MTX naïve Subjects With Active Psoriatic Arthritis
8. NCT03796858 - CNTO1959PSA3003 - Phase 3b, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Guselkumab Administered Subcutaneously in Participants With Active Psoriatic Arthritis and an Inadequate Response to Anti-Tumor Necrosis Factor Alpha (Anti-TNFα) Therapy
9. NCT02319759 - CNTO1959PSA2001 - A Phase 2a, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab in the Treatment of Subjects With Active Psoriatic Arthritis
10. NCT03158285 - CNTO1959PSA3002 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab Administered Subcutaneously in Subjects With Active Psoriatic Arthritis
11. NCT03162796 - CNTO1959PSA3001 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab Administered Subcutaneously in Subjects With Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti-TNF Alpha Agents

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

Research Proposal

Project Title

EXploring SEx-related Mechanisms of Psoriatic Arthritis response to advanced therapies (EXSEMP): Individual participant data (IPD) meta-analysis

Narrative Summary:

Women living with psoriatic arthritis are less likely to respond to biologic therapies, which are effective, yet, expensive type of treatment for arthritis. Our study will explore the reasons for this finding by analyzing data from clinical trials that evaluated biologic therapies in psoriatic arthritis (PsA). We will investigate whether certain types of biologic treatments are more effective and safer in women with PsA. Additionally, we will study whether selected factors, such as levels of inflammation and body weight, could explain the lower response to treatment in women. The results of our study could contribute to the development of sex-specific recommendations for prescribing biologic

Scientific Abstract:

Background: Limited information exists on sex difference in response to advanced therapies in psoriatic arthritis (PsA).
Objective: To estimate the magnitude and causes of sex-related differences in efficacy and safety of advanced therapies in PsA randomized clinical trials (RCTs).
Study Design: We will perform a meta-analysis of individual participant data (IPD)
Participants: Adult patients with active PsA who participated in RCTs of the following classes of medications: TNF inhibitor (i), IL-17i, IL-12/23i, IL-23i, PDE4, JAKi, and TYK2i.
Primary outcomes: Primary outcome will be American College of Rheumatology (ACR) 20/50/70 response in males vs. females within and across drug classes.
Secondary outcomes: Achievement of minimal disease activity state, resolution of dactylitis and enthesitis, rates of adverse effects analyzed by sex for each drug class. Drug persistence and cause of drug discontinuation will also be analyzed by sex.
Statistical analysis: We will perform a two-stage individual participant level meta-analysis. First, the data from each study will be analyzed separately in order to obtain aggregate (summary) data of interest. In stage two, these estimates will be combined using fixed- or random-effects meta-analysis models. The differences in males and females in study outcomes will be reported as Odds Ratio and 95% confidence intervals.

Brief Project Background and Statement of Project Significance:

Background
While Psoriatic arthritis (PsA) is equally distributed across sexes notable differences exist in response to advanced therapies between males and females1. Real world data have shown significant differences in effectiveness of biologic therapies between male and female patients with PsA2-6. Females are less likely to achieve remission, are prone to develop adverse effects (AE) and tend to discontinue treatments earlier than males. Thus, it is surprising that little attention has been given so far to understanding which sex/gender-related mechanisms explain these disparities.
While real-world data is important, randomized controlled trials (RCTs) provide unbiased evidence regarding the efficacy and safety of therapeutic agents. In a recent meta-analysis of RCTs, we found substantial under-reporting of efficacy and safety end-points by sex7. Only 33% and 4% of 54 trials reported efficacy and safety end-points by sex, respectively. Such under-reporting precludes an accurate estimation of the effect of sex on treatment effectiveness. More importantly, we found that sex-differences in treatment response vary by drug class. Significantly lower rates of ACR20 and ACR50 response were found in females among all biologic drugs, including TNF inhibitor (i), IL-17i, IL-12/23i and IL-23i, however, no such sex differences in response to JAK/TYK2i were found7.

Rationale
The limitations and evidence gaps described above highlight the need for more rigorous, in-depth analyses focusing on comparative, sex-related differences in the effectiveness of advanced therapies in PsA and their and underlying mechanisms. An Individual participant data (IPD) meta-analysis overcomes the problems of aggregate data meta-analysis. By accessing and analyzing raw, participant-level data from each trial, IPD allows for standardizing the inclusion criteria, analysis across studies, and obtaining secondary end-points that had not been provided in the trial publication. Most importantly, IPD allows direct modelling of individual-level interactions within studies which allows for mediation analysis8.

Research Hypothesis
Based on our aggregate data meta-analysis and real-world studies, we hypothesize that sex differences exist in efficacy and safety of advanced therapies in PsA RCTs. The magnitude of these differences across the different drug classes remains unknown, but it is expected be higher biologics drugs. Additionally, we hypothesize that sex-related participant-level factors mediate these differences in drug response. Our proposed IPD analysis of RCT data will allow assessing our hypothesis that participant-level characteristics, including higher BMI in females, difference in pain

perception and systemic inflammation, and tendency for immunogenicity, mediate the observed sex differences.

Specific Aims of the Project:

Overall Objective
Our overall objective in this IPD meta-analysis is to study sex-differences in efficacy and safety of advanced therapies in PsA RCTs and to understand the underlying mechanisms of these sex-differences. By evaluating selected sex-related, individual patient characteristics we hope to gain insights to the mediating factors of these sex differences in drug effectiveness. Ultimately we hope to provide novel information to inform sex-specific drug prescription that will ultimately optimize patient care

SPECIFIC AIMS
This IPD meta-analysis will address the following aims
1) To estimate the magnitude of sex differences in efficacy, safety, and persistence of advanced therapies between male and female patients with PsA participating in RCTs within and across drug classes.
2) To assess the mediating effect of the following patient-level factors on drug efficacy in males and females: pain, BMI, pharmacokinetics and immunogenicity, dosing, and co-medication.
3) To study the effect of menopausal state and use of sex hormone replacement therapy on trial outcomes among female patients

Study Design:

Meta-analysis (analysis of multiple trials together)

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

Summary-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research Methods

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

INCLUSION CRITERIA
1) RCTs in adult patients with PsA for peripheral arthritis
2) Trial assessed the efficacy of the following drugs vs. placebo or another DMARD: adalimumab, infliximab, etanercept, certolizumab, golimumab, secukinumab, ixekizumab, ustekinumab, apremilast, abatacept, tofacitinib, upadicitinib, filgotinib, guselkumab, risankizumab
3) Access to sex desegregated data of efficacy and safety end points either individual level data or aggregate level (via primary publication)

EXCLUSION CRITERIA
1) Non-randomized studies;
2) Trials that lasted less than 12 weeks;
3) Studies that compared bio-similar DMARDs to the corresponding reference product because these studies were typically designed as non-inferiority trials.

We identified a total of 40 trials that meet inclusion criteria including 11 TNFi trials, 9 IL-17i trials, 4 JAK/TYK2i trials, 4 IL-12/23i trials, 6 IL-23i trials, 5 PDE4i trials, and 1 CTLA4i trial.
Access to some of these trials can be requested through Vivli, YODA and Clinical Study Data Request or directly from the study sponsor. When individual participant data are not available we will use aggregate level data for the meta-analysis.

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

Primary outcome: American College of Rheumatology (ACR) 20/50/70 response - this will require information on tender joint count, swollen joint count, pain, patient global, physician global. HAQ, CRP
Secondary end points: Minimal disease activity state: this will require (in addition to the above): enthesitis score, Psoriasis Area and Severity Index (PASI), dactylitis, SF-36, FACIT-fatigue.
Adverse effects (any, severe, death, infection)
Persistence on the study medication (date of discontinuation and cause)

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

Aim 1: Sex of patients (male/female)
Aim 2: Body mass index (BMI), pain level, use of methotrexate, CRP, drug level, development of anti drug antibody
AIM 3: Menopausal state

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

age, ethnicity, duration of PsA, use of corticosteroid, prior use of biologics, co-morbidities,

Statistical Analysis Plan:

Due to limited space we provide here a brief summary of the analysis plan. A detailed statistical analysis plan is attached as a separate file.

We will perform a two-stage IPD meta-analysis. First, the IPD from each study is analyzed separately to obtain aggregate (summary) data of interest (e.g. effect estimate and its confidence intervals). Subsequently, in stage two, these data are combined using an appropriate fixed- or random-effects meta-analysis model. This approach was selected as we plan to use several data platforms and cannot analyze all trials within a single platform. Additionally, the two-stage approach is less computationally intense and is not prone to convergence problems.

For Aim 1: The main statistical analysis will be conducted according to the intention-to-treat (ITT) principle. For each trial, we will calculate the rates of end points by sex and intervention arm. We will use generalized linear mixed-effects regression models with repeated measures, including fixed effects of sex, treatment arm, and time point as covariates. The odds ratio (OR) of achieving study outcomes for various time points (and their confidence intervals) will be used in stage 2, which will employ a meta-analysis to compare efficacy end-points by sex. A similar statistical approach will be used to assess the effect of sex on rates of adverse effects and drug persistence.

For Aim 2: We will study potential sex-related attributes that contribute to differences in response by performing a mediation analysis. We will investigate the following participant-level variables as sex-specific mediators of drug efficacy: pain level, BMI, concomitant methotrexate use, CRP level, drug levels, and anti-drug antibodies. We will first assess whether the distribution of the proposed mediators vary by sex. Then, we will conduct a series of regression models with sex as a co-variate in addition to attributes related to the mechanism of interest and assess to what extent the effect of sex is modified.

For Aim 3: We will use a similar approach as described above using menopause status as primary predictor of response among females.

Software Used:

RStudio

Project Timeline:

Obtaining access to participant level data and signing contracts - via Vivli/YODA/CPSD and Amgen platform - September 2024
Data checking and standardization - June 2025
Summary of results AIM 1 - September 2025
Summery of results AIM 2 - June 2026
Summary Results AIM 3 - December 2026

Dissemination Plan:

- Presentation of summary results as abstracts in rheumatology conference abstracts (expected audience rheumatology clinicians and researchers)
- Publication of manuscripts in peer reviewed medical journals (rheumatology or general medicine)

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Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2024/05/Protocol-V4-May2024.docx