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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?: Colleague

Conflict of Interest

http://yoda.yale.edu/system/files/coi-lihi_eder.pdf
http://yoda.yale.edu/system/files/coi_zahi.pdf
http://yoda.yale.edu/system/files/yoda_coi_ao.pdf
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http://yoda.yale.edu/system/files/signed_yoda_project_cui_form_for_data_requestors_2018.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. 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
2. NCT01009086 - A Study of the Safety and Effectiveness of Ustekinumab in Patients With Psoriatic Arthritis
3. NCT01077362 - A Study of the Safety and Efficacy of Ustekinumab in Patients With Psoriatic Arthritis With and Without Prior Exposure to Anti-TNF 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

The efficacy of biologic medications in improving depressive symptoms in patients with PsA – Patient-level meta-analysis

Narrative Summary:

In this study we aim to compare the effect of three classes of medications used for the treatment of psoriasis and psoriatic arthritis in improving depressive symptoms in patients participating in clinical trials. The three classes of medications include: TNF inhibitors, IL-12/IL-23 inhibitors and IL-17 inhibitors.
We will combine data from clinical trials that assessed the effect of the above mentioned drugs. The study outcome will be the change in depressive symptoms that will be measured by a component of a quality of life questionnaire. The results of the study will assist physicians treating patients with PsD in selecting the appropriate class of medication.

Scientific Abstract:

Background: Psoriatic arthritis (PsA) is frequently associated with other co-morbidities including depression. Systemic inflammation is associated with depression, thus suppression of inflammation may have a beneficial effect on depressive symptoms.

Objective: To compare the efficacy of TNF inhibitor and IL-12/IL-23 inhibitor in improving depressive symptoms among patients with PsA participating in clinical trials.

Study Design: We will conduct a patient level meta-analysis of data from randomized placebo-control clinical trials assessing the efficacy of the following medications in patients with PsA: golimumab (TNF inhibitor) and ustekinumab (IL-12/IIndividual-patient data from each trial will be merged into a single dataset using common variables including demographics, co-morbidities including depression, measures of psl-23 inhibitor).

Participants: Patients with active PsA from clinical trials.

Main Outcome Measures: The primary outcome of the study is the change in depressive symptoms in study drug arm compared with the placebo arm. The Short-Form Health Survey (SF-36) mental component summary (MCS) score will be used assess the change in depressive symptoms over time.

Statistical Analysis:
Analyses will be conducted in the randomized set including all patients randomized to the study with complete data. The study outcome will be reported at all time points during the double-blind portion of the by exposure to the study drug or placebo.
The effect of each drug on depressive symptoms will be assessed using multivariable regression analysis.

Brief Project Background and Statement of Project Significance:

Depression has wide reaching affects; it has been associated with an increased risk for cardiovascular disease, weight gain, increased musculoskeletal pain, and poor quality of life in the general population1, 2. These factors can have a significant impact on the course of other diseases including psoriasis and psoriatic arthritis (PsA). Psoriasis is common inflammatory skin disorder affecting 2-4% of the population3, 4. PsA is a chronic and often debilitating inflammatory arthritis affecting nearly one third of patients with psoriasis5, 6. Psoriatic disease (PsD), including both psoriasis and PsA, is associated with a number of comorbidities. Depression is among the most impactful on quality of life but has been given little attention in the literature7. However, recently, the awareness of this issue was heightened by concerns regarding drug-induced depression among patients with PsD participating in clinical trials. These events have underscored the importance of better understanding the relationship between depression and PsD and the impact of therapy for PsD on depression.
Depression is common among patients with PsA. The association between PsD and depression has been acknowledged for many years in the dermatology literature5, 6, 8. Patients with PsD may have debilitating joint disease with pain, fatigue, reduced ability to work, and embarrassment about joint deformities and skin disease. All of these factors can lead to depression. However, depression may also be related to the pathophysiology of PsD rather than soley a result of the clinical manifestations of PsD. In fact, depression may precede disease symptoms, particularly for PsA. Patients with psoriasis who were depressed were more likely to develop PsA than patients without depression9.
Inflammation and Depression. While depression has been primary thought of as a disregulation of neurotransmitters, recent evidence suggests that there are multiple processes at play, part of which is immune activation and inflammation. Previous meta-analyses have found that pro-inflammatory cytokines are associated with major depression. There is an overlap between some of the pro-inflamamtory mechnisms that have been linked with depression and PsD10,11. Thus, therapy for PsD may also have implications for depression. There is little data about the anti-depressant effects of biologic medications in humans10.
Significance: Despite this potential direct connection between the two disorders and the important clinical implications, little is known about the impact of effective control of inflammation on depressive mood in patients with psoriasis and PsA and the direct impact of therapies for PsD on depression. Furthermore, certain drugs may not be advantageous for patients with PsD and depression. Currently, there is no data about the relative efficacy of the various biologic medications in improving depressive symptoms in patients with psoriasis and PsA. The goal of this application is to examine how depression changes with treatment of PsD.

Specific Aims of the Project:

We propose an individual-level meta-analysis using data from clinical trials among patients with PsA. We aim to examine how depressive mood changes with therapy intervention and the time course over which it changes. More specifically, we will compare the efficacy of the following two biologic medications for PsA: golimumab (TNF inhibitor) and ustekinumab (IL-12/IL-23 inhibitor) in improving depressive symptoms among patients with PsA

participating in clinical trials.

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 populationsParticipant-level data meta-analysisParticipant-level data meta-analysis using only data from YODA Project

Research Methods

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

We will conduct a patient level meta-analysis of data from phase 2 and 3 randomized double-blinded placebo-control clinical trials assessing the efficacy of the following classes of medications in patients with psoriatic arthritis (PsA): 1) TNF inhibitors (golimumab); 2) IL-23/IL-12 inhibitor (ustekinumab);
The study population will include patients with active PsA that were treated with one of the 2 classes of biologic medications indicated above.

Inclusion criteria
1) Randomized placebo-control clinical trial in patients with active PsA
2) Phase 2 or 3 trials

Exclusion criteria
1) Open label study/extension period of RCTs
2) Phase 1 studies
3) Lack of SF-36 questionnaire response

For each trial the analysis will include all patients who were randomized to receive the study drug or placebo. Patients in the study drug arm will be compared to patients in the placebo arm. The comparison will include information collected during the double-blind portion of the trial. Information from the extension period of the trial will not be included in the analysis.

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

The primary outcome of the study is the change in depressive symptoms in study drug arm compared with the placebo arm. The Short-Form Health Survey (SF-36) mental component summary (MCS) score will be used assess the change in depressive symptoms over time.
The gold standard for assessment of depression is a psychiatric evaluation, however, various questionnaires were found to detect depression with reasonable sensitivity and specificity. The SF-36 is a generic measure of quality of life that is commonly measured in clinical trials to assess quality of life. A recent study found that the SF-36 MCS with a threshold of ?38 could be used to detect major depressive disorder in rheumatoid arthritis patients with a sensitivity of 87%, sensitivity of 80% and accuracy of 83%.12
A secondary analysis will use the SF-36 MCS to classify patients based on depression status. We will use a cut-off of SF-36 MCS?38 to identify patients with depression. We will perform sensitivity analyses with cut-off points of MCS?35 and ?40 as alternative definitions of depression. We will assess the change in depression status during t

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

The primary predictor of the study will be the use of a biologic medication. The reference group will be the use of placebo. For each trial the analysis will include all patients who were randomized to receive the study drug or placebo. Patients in the study drug arm will be compared to patients in the placebo arm. The comparison will include information collected during the double-blind portion of the trial. Information from the extension period of the trial will not be included in the analysis.

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

Individual patient data from each trial will be merged into a single dataset using common variables including demographics (age, sex), co-morbidities including depression, disease duration, measures of psoriasis and PsA disease activity including tender and swollen joint counts, dactylitis, enthesitis and psoriasis area and severity

index, laboratory inflammatory markers including ESR and CRP, use of study drug and its dose or placebo, concomitant medications including disease modifying anti rheumatic drugs, non-steroidal anti-inflammatory medications, corticosteroids and anti-depressive medications and patient reported outcomes including SF-36 (physical and mental component scores), Health Assessment Questionnaire, patient global assessment of disease activity and pain scores.

Statistical Analysis Plan:

We will perform the analysis in the combined dataset that will include all studies with complete individual-patient level data.
Analyses will be conducted in the randomized set including all patients randomized to the study with complete data. The study outcome will be reported at all time points during the double-blind portion of the study by exposure to the study drug or placebo.
Initially, each trial will be analyzed separately. Subsequently, the effect of each drug will be assessed individually and finally the effect of each drug class (TNFi or IL-12/IL-23) on depression will be assessed.
We will descriptively report the mean change in SF-36 MCS scores by study arm. Univariate linear regression models will be used to assess the effect of each study drug/drug class on the change in SF-36 MCS scores at the two follow up time points. Each model will also include a study indicator to account for population differences across studies. To assess what is the impact of baseline depression status on the effect of study drug/drug class on the change in Sf-36-MCS, a subgroup analysis by baseline depression status (patients meeting the criteria for depression based on SF-36-MCS cut-off) will be conducted. Subsequently, multivariable regression analyses will be performed to assess the effect of the study drug/drug class on the change in SF-36-MCS after adjusting for the following variables: age, sex, BMI, concomitant disease modifying anti-rheumatic drugs, previous biologic treatment, number of tender and swollen joints, minimal disease activity status, physician global assessment and PASI.
In addition we will consider depressive status as a categorical outcome by classifying patients to Depression or no-Depression based on a cut off of SF-36 MCS?38.
We will descriptively report the number of patients meeting the criteria for depression by study arm and their demographic characteristics. We will next descriptively report the proportion of patients with depression at baseline who no longer meet criteria for depression at the two follow up time points. Similarly, we will report the number of patients without depression at baseline that become depressed in each group. We will use logistic regression models with depression status as the outcome and study drug/drug class as the primary predictor and baseline depression status as a model co-variate to assess the impact of the primary predictor on transition from baseline depression status to no meeting depression criteria at the two follow-up points. As described above, multivariable regression analyses will also be performed using the co-variates outlined above.
One of the advantages of the trials is that most include more than one dose of the study drug allowing for examination of dose effect. We will initially analyze each drug dose separately. We will assess whether a dose-response effect on depressive symptoms exists by comparing the effect sizes from the regression models across the different drug doses. We will then combine the different doses to a single group.
Sensitivity analyses: In studies in which depression indicators, either patient-reported depression, physician-reported depression or depression indices are included, we will report the results using both definitions of depression.
In studies with <10% missing data, can use multiple imputation to see if results are different (or use this as primary. A complete case analysis will be conducted. We will examine whether there are differences at baseline among those with and without missing data.
The primary analysis will be performed according to the intention to treat principle with the outcome measure assessed at the first escape point (approximately 12 to 16 weeks). A secondary analysis will assess the outcome at the second follow up period (24 weeks). A sensitivity analysis will be performed per-protocol at each follow up time point.

Project Timeline:

The project will be completed over a period of 12 months. We have already obtained an exemption from ethics approval form the Women’s College Hospital REB (REB # 2017-0007-E Research Ethics Exemption Letter). The expected timeline:
March 2017 - Submit Requests for Data
December 2017 – completion of data analysis
March 2018 – Finish drafting the manuscript and submission for publication

Dissemination Plan:

Knowledge dissemination strategies of our results will include a peer-reviewed and presentations at local and national and international medical conferences. We will also partner with patient organizations to disseminate the results of our study to the psoriasis and arthritis communities through publication in their websites (e.g., Arthritis Alliance of Canada, Arthritis Society, Canadian Association of Psoriasis Patients).

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