Principal Investigator

First Name: Glen
Last Name: Hazlewood
Degree: PhD, FRCPC, MD, BSc
Primary Affiliation: University of Calgary
E-mail: gshazlew@ucalgary.ca
Phone number:
Address:

City: Calgary
State or Province: Alberta
Zip or Postal Code: T2N 1N4
Country: Canada

General Information

Key Personnel (in addition to PI):

First Name: George
Last name: Wells
Degree: PhD, MD, BSc
Primary Affiliation: University of Ottawa
SCOPUS ID:

First Name: Rob
Last name: Deardon
Degree: PhD, MSc, BSc
Primary Affiliation: University of Calgary
SCOPUS ID:

First Name: Rachelle
Last name: Buchbinder
Degree: FAHMS, PhD, MSc, FRACP, MBBS
Primary Affiliation: Monash University
SCOPUS ID:

First Name: Samuel
Last name: Whittle
Degree: MClinEpi, FRACP, MBBS
Primary Affiliation: Monash University
SCOPUS ID:

First Name: Peter
Last name: Tugwell
Degree: MSc, FRCPC, PhD, MD
Primary Affiliation: University of Ottawa
SCOPUS ID:

First Name: Shannon
Last name: Kelly
Degree: PhD (current), MSc, MA
Primary Affiliation: University of Ottawa
SCOPUS ID:

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

First Name: Mohammed
Last name: Kamso
Degree: PhD (current), MSc, BA
Primary Affiliation: University of Calgary
SCOPUS ID:

First Name: Jesse
Last name: Elliot
Degree: PhD, MSc
Primary Affiliation:
SCOPUS ID:

First Name: Jocelyn
Last name: Thomas
Degree: BSc, MSc (trainee)
Primary Affiliation: University of Calgary
SCOPUS ID:

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: CIHR (pending review)
How did you learn about the YODA Project?: Other

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_buchbinder.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_tugwell.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_deardon.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_whittle.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_jthomas.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_wells.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_kelly.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_jelliot.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_hazlewood.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_kamso_1.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. 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
2. 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)
3. NCT00361335 - C0524T12 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy
4. NCT01248780 - C0524T28 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Golimumab in the Treatment of Chinese Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

5. NCT00269867 - C0168T22 - A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody (cA2) in Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment
6. NCT00973479 - CNTO148ART3001 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, an Anti-TNFalpha Monoclonal Antibody, Administered Intravenously, in Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy
7. 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
8. NCT00202852 - P04280 - A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody (cA2) in Korean Patients With Active Rheumatoid Arthritis Despite Methotrexate
9. C0168T14 - Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis
10. NCT01962974 - CNTO148ART3003 - A Golimumab Phase 3b, Multicenter, Assessment of Intravenous Efficacy in Rheumatoid Arthritis Subjects Who Have Diminished Disease Control Despite Treatment With Infliximab (REMICADE®)
11. NCT00036387 - C0168T41 - A Randomized, Double-blind Trial of the Safety of Anti-TNF Chimeric Monoclonal Antibody (Infliximab) in Combination With Methotrexate Compared to Methotrexate Alone in Patients With Rheumatoid Arthritis on Standard Disease-modifying Anti-Rheumatic Drug

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

Research Proposal

Project Title

Disease-modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis incorporating individual patient data

Narrative Summary:

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint pain, swelling, fatigue, and impaired quality of life. In this study, we will compare the benefits and harms of treatment options for RA by conducting a network meta-analysis (NMA) that incorporates individual patient data (IPD). This will allow us to provide more robust and personalized data to help patients and their physicians choose between all the treatment options available.

Scientific Abstract:

Background. Rheumatoid arthritis (RA) is a chronic autoimmune form of arthritis that can affect adults of any age. People living with RA experience pain and swelling in their joints, fatigue, and difficulty functioning. Medications, called disease-modifying anti-rheumatic drugs (DMARDs), are used to control joint inflammation. With over 20 different DMARDS available, we need high-quality evidence comparing RA treatment options.

Objective. To estimate the comparative efficacy and safety of DMARD treatment options through network meta-analyses combining individual and summary level data.

Study Design. We will conduct Bayesian network meta-analyses of randomized trials of DMARD therapy for RA, including individual-level patient data, where available.

Participants. The eligibility criteria for the NMAs are randomized trials in adult (Age >18) participants with RA that compare any DMARD to placebo/no treatment or another DMARD.

Main Outcome Measure(s). We will examine six outcomes in our analyses: 1) American College of Rheumatology

(ACR)-50 response; 2) radiographic progression; 3) withdrawals due to adverse events; 4) Clinical disease activity index (CDAI) low disease activity (<= 10); 5) CDAI remission (<= 2.8); 6) Serious adverse events.

Statistical Analysis. We will conduct Bayesian random-effects arms-based meta-analyses for each outcome, using models that account for the correlation in multiple-arm trials [18]. To incorporate the individual patient data, a hierarchical model will be constructed, following the approach of Jansen et al [19].

Brief Project Background and Statement of Project Significance:

Rheumatoid arthritis (RA) is an autoimmune disease that affects between 0.2% to 0.4% of adults [1]. People living with rheumatoid arthritis experience joint pain, stiffness, impaired function, fatigue and significantly decreased quality of life. While rheumatoid arthritis cannot be cured, there are now many effective medications available. These medications are referred to as disease-modifying antirheumatic drugs (DMARDS) and are the mainstay of RA treatment. They work to control the underlying inflammation that is responsible for peoples' symptoms. In doing so, they also protect the joints from damage.

There are now over 20 different DMARDs available for RA. DMARDs can be divided into different categories, based on how they are made and what parts of the immune system they target [2]. Conventional synthetic DMARDs and targeted synthetic DMARDs are both 'traditional' medications, in the sense that they are synthetically made. The difference is that the latter were developed with a specific target of the immune system (e.g. cell type or protein) in mind. These medications contrast with biologic DMARDs, which are made biologically (e.g. antibodies) and are much more complex in their structure. Given their complex structure, it is not possible to exactly reproduce biologics. As such, biologics are typically divided into biologic originator or biosimilar DMARDs, according to whether they were the first or subsequent manufacturers.

Given the many different choices of DMARDs available, we need high-quality evidence that compares the benefits and harms. Network meta-analysis is a method whereby every randomized trial that has been conducted on these treatments is analyzed together as a 'network' [3]. A main benefit of network meta-analysis is that it allows all treatments to be compared against one another. Our research group has published several Cochrane reviews of network meta-analyses comparing DMARD treatments in rheumatoid arthritis [4-8]. Recently, we have transitioned these reviews to a 'living' mode, whereby the evidence will be updated continuously over time, to take into account new trials that are published [9].

While our network meta-analyses allow comparisons between treatments, the comparisons are made using average (group-level) data from the trials. In this study, we will conduct a network meta-analysis using the raw (individual level) data from the clinical trials, where this data is available. This has two main advantages. First, it will allow us to determine whether patients with certain characteristics may respond better to one drug or another. Second, it will allow us to ensure each trial is analyzed using similar approaches. Overall, this will allow us to provide more robust and personalized data to help patients and their physicians choose between all the DMARD options available.

Specific Aims of the Project:

Our primary objective is to develop predictive models that can better classify the benefits and harms of different DMARDs in adults with rheumatoid arthritis: 1) who have had an inadequate response to conventional synthetic DMARDs; 2) who have had an inadequate response to anti-tumor necrosis factor therapy. Our hypothesis is that certain simple clinical characteristics, that would be available to physicians at the time of the treatment decision, can be used to help distinguish the available treatment options.

What is the purpose of the analysis being proposed? Please select all that apply.
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources
Research on clinical prediction or risk prediction

Research Methods

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

Data will be sourced from Vivli and YODA.
The eligibility criteria for the NMAs are randomized trials in adult (Age >18) participants with rheumatoid arthritis that compare any DMARD to placebo/no treatment or another DMARD. DMARDs include conventional synthetic, biologic, biosimilar and targeted synthetic DMARDs. The full list of eligible DMARDs is published in the protocol [9]. In the group-level NMA, separate NMAs are planned according to the prior treatment failed: DMARD-naïve (no prior failed treatment); inadequate response to conventional synthetic DMARDs; inadequate response to biologic/targeted synthetic therapy. For this project, we will add individual-level trial data to the NMAs for: 1) DMARD options after an inadequate response to conventional synthetic DMARDs; 2) DMARD options after failure of anti-tumor necrosis factor therapy. We have excluded the NMA in DMARD-naïve patients, as the available individual patient-level data is largely confined to second-line and advanced therapies. Similarly, we restricted the second NMA to patients who have failed TNF therapy as this represents the majority of the trials with individual patient-level data.

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

We will examine six outcomes: 1) American College of Rheumatology (ACR)-50 response; 2) radiographic progression; 3) withdrawal due to adverse events; 4) Clinical disease activity index (CDAI) low disease activity (<= 10); 5) CDAI remission (<= 2.8); 6) Serious adverse events. The first three outcomes match the three major outcomes of our Cochrane protocol [9]. They capture important treatment benefits and harms and are commonly measured and reported in clinical trials. CDAI was added as an additional outcome to assess treatment benefit, similar to a recently published NMA in RA [10]. It is well validated and does not require any laboratory tests, making it easy to apply in clinical practice. Serious adverse events were included as an additional measure of harm. This is also an outcome measure in our Cochrane protocol [9].

Each outcome will be evaluated at trial end, defined as the end of the randomized period, matching our group-level NMA [9]. As a secondary analysis, we will also analyze outcomes at 6 months. For the 6-month analysis, we will extract data at the closest time-point to 6 months, accepting windows of ? 20 weeks and <39 weeks, to match our group-level NMAs.

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

The main predictor variable will be the treatment received. The six outcome measures are defined above.
The following classes of therapy will be included: conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs); anti-tumor necrosis factor (TNF) inhibitors; interleukin-6 (IL6) inhibitors; abatacept; rituximab; janus kinase (JAK) inhibitors.

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

We will explore whether there is an association with baseline variables and treatment effects through meta-regression:
-age
-sex
-seropositivity (either rheumatoid factor or anti-CCP positive)
-baseline disease severity: DAS-28-CRP, or DAS-28-ESR if DAS-28-CRP not available [15]
-disease duration
-baseline functional limitation or disability, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) [16] or modified HAQ (mHAQ) [17]

Statistical Analysis Plan:

For each outcome we will first replicate the original published results of the trial, reaching out to the study sponsor if additional information is needed. For our main network meta-analyses we will analyze the outcomes in their original published form. This will allow us to directly compare the results of the individual patient data network meta-analyses to the group-level network meta-analysis, while allowing for the exploration of effect-modification with the individual patient data.

The network meta-analyses with the individual patient data will follow our published protocol for the group-level

network meta-analyses [9], with modifications to incorporate the individual-patient level data. We will conduct Bayesian random-effects arms-based meta-analyses for each outcome, using models that account for the correlation in multiple-arm trials [18]. To incorporate the individual patient data, a hierarchical model will be constructed, following the approach of Jansen et al [19]. For each trial with individual patient data, the treatment effect will be modelled using the individual patient data, then the summary estimate is included in the network meta- analysis, along with the other summary estimates, where only group-level data is available.

For the meta-regression models, we will specify covariate effects for the treatment effect relative to placebo. This will be done again in a hierarchical model, using individual patient data where available, or mean/median baseline values for trials where only group-level data is available. Separate covariate effects will be specified for each class of therapy relative to placebo. If a trial does not contain a placebo arm, the trial will still be included in the network, but no covariate effect will be specified. If a trial contains multiple arms, covariate effects will be specified for each treatment arm relative to placebo.

A multivariable meta-regression model will be developed in a stepwise fashion, using measures of model fit (residual deviance, Deviance Information Criterion (DIC)) to compare between models. For the base models, we will include a covariate effect for the baseline placebo response rate in each trial. In meta-regression for our prior network meta-analysis, we previously demonstrated a large, statistically significant effect for the placebo response rate [decrease in odds ratio of 0.59 times (95% credible interval: 0.43 to 0.75) for every 10% increase in the response rate for methotrexate], although the adjusted treatment effects were similar to the unadjusted effects [4, 20]. We will use the modelled response rate as opposed to the actual response rate in each trial to limit the effect of regression to the mean [21]. To this base model, we will then conduct additional meta-regression analyses, adding in a covariate effect for each of the variables outlined above, one at a time. Finally, a multivariable model will be developed including all covariates, while ensuring at least 10 observations in each cell, to avoid over-fitting. Given that health assessment questionnaire-disability index (HAQ-DI) and disease activity score – 28 (DAS-28) are highly correlated, we will reduce the final model by removing one of these variables, choosing the model with the best fit.

In our Bayesian analysis, uninformative prior probability distributions will be used for all parameters. The prior distribution around the random effect will be varied in sensitivity analyses, as discussed below. We will use Markov chain Monte Carlo sampling to obtain samples from posterior distributions, with 10,000 burn-in iterations followed by 10,000 monitoring iterations, after confirming convergence. Convergence will be assessed by analyzing the differences between the Markov chains. Specifically, we will run three chains, inspect the sampling history plots, and calculate Gelman-Rubin-Brooks (GBR) statistics [22]. We will assess model fit by using residual deviance and DIC.
Software Used:
R

Project Timeline:

Anticipated start date: Dec 1, 2020
Analysis completion date: Sept 1, 2022
Manuscript drafted & submitted for publication: Dec 1, 2022
Results reported back to YODA project: Dec 1, 2022

Dissemination Plan:

We will publish our results in peer-reviewed journals and present the findings at academic conferences. The project is intimately linked to our living Cochrane NMA [9] and living Canadian Rheumatology Association (CRA) treatment recommendations for RA.

Bibliography:

1: Safiri S, Kolahi AA, Hoy D, Smith E, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. Ann Rheum Dis. 2019;78(11):1463-71.
2: Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewe R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Ann Rheum Dis. 2014;73(1):3-5.
3: Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med. 2002;21(16):2313-24.
4: Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJ, Bombardier C. Methotrexate monotherapy and

methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. Cochrane Database Syst Rev. 2016(8):CD010227.
5: Singh JA, Hossain A, Mudano AS, Tanjong Ghogomu E, Suarez-Almazor ME, Buchbinder R, et al. Biologics or tofacitinib for people with rheumatoid arthritis naive to methotrexate: a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2017;5:CD012657.
6: Singh JA, Hossain A, Tanjong Ghogomu E, Mudano AS, Maxwell LJ, Buchbinder R, et al. Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2017;3:CD012591.
7: Singh JA, Hossain A, Tanjong Ghogomu E, Mudano AS, Tugwell P, Wells GA. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA). Cochrane Database Syst Rev. 2016;11:CD012437.
8: Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011(2):CD008794.
9: Hazlewood G, Whittle S, Kamso M, Akl E, Wells G, Tugwell P, et al. Disease-modifying anti-rheumatic drugs for rheumatoid arthritis: a systematic review and network meta-analysis. Cochrane Database of Systematic Reviews. 2020;3(3):CD013562.
10: Janke K, Biester K, Krause D, Richter B, Schurmann C, Hirsch K, et al. Comparative effectiveness of biological medicines in rheumatoid arthritis: systematic review and network meta-analysis including aggregate results from reanalysed individual patient data. BMJ. 2020;370:m2288.
11: 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;38(6):727-35.
12: Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 2005;23(5 Suppl 39):S100-8.
13: Ory PA. Interpreting radiographic data in rheumatoid arthritis. Ann Rheum Dis. 2003;62(7):597-604.
14: Markusse IM, Landewe R, Wolterbeek R, Ho M, Jenkins M, van der Heijde D. Linear extrapolation of missing radiographic change scores in clinical trials does not spuriously overestimate group radiographic changes in rheumatoid arthritis. Rheumatology (Oxford). 2016;55(7):1295-300.
15: Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44-8.
16: Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol. 1982;9(5):789-93.
17: Pincus T, Yazici Y, Bergman M. Development of a multi-dimensional health assessment questionnaire (MDHAQ) for the infrastructure of standard clinical care. Clin Exp Rheumatol. 2005;23(5 Suppl 39):S19-28.
18: Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making. 2013;33(5):607-17.
19: Jansen JP. Network meta-analysis of individual and aggregate level data. Res Synth Methods. 2012;3(2):177-90.
20: Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe D, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: abridged Cochrane systematic review and network meta-analysis. BMJ. 2016;353:i1777.
21: Sharp SJ, Thompson SG, Altman DG. The relation between treatment benefit and underlying risk in meta-analysis. BMJ. 1996;313(7059):735-8.
22: Brooke SP, Gelman A. General Methods for Monitoring Convergence of Iterative Simulations. Journal of Computational and Graphical Statistics.7(4):434-55.