Principal Investigator

First Name: Vijesh
Last Name: Bhute
Degree: PhD
Primary Affiliation: Imperial College London
E-mail: vijeshbhute@gmail.com
Phone number: +447713962761
Address: ACEX 1M17A, Imperial College London, South Kensington Campus

City: London
State or Province: London
Zip or Postal Code: SW7 2AZ
Country: United Kingdom

General Information

Key Personnel (in addition to PI):
First Name: Isabelle
Last name: Ho
Primary Affiliation: Imperial College London

First Name: Megan
Last name: Caunce
Primary Affiliation: Imperial College London

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?: Internet Search

Conflict of Interest

https://yoda.yale.edu/system/files/sv_6m4tghhxg7w7uxe-r_a3pe4maaanauztf.pdf
https://yoda.yale.edu/system/files/yoda_form_isabelle.pdf
https://yoda.yale.edu/system/files/yoda_form_megan.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. 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
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. 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)
4. 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
5. 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
6. 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
7. NCT00236028 - C0168T29 - 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
8. 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
9. 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
10. C0168T14 - Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis
11. NCT01604343 - CNTO136ARA3002 - A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of CNTO 136 (Sirukumab), a Human Anti-IL-6 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Rheumatoid Arthritis Despite DMARD Therapy
12. NCT01606761 - CNTO136ARA3003 - A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of CNTO 136 (Sirukumab), a Human Anti-IL-6 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Rheumatoid Arthritis Despite Anti-TNF-Alpha Therapy
13. NCT02181673 - CNTO148PSA3001 - A Study of Golimumab in Participants With Active Psoriatic Arthritis
14. NCT01004432 - CNTO148ART3002 - Golimumab in Rheumatoid Arthritis Participants With an Inadequate Response to Etanercept (ENBREL) or Adalimumab (HUMIRA)
15. 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®)
16. 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
17. NCT01689532 - CNTO136ARA3001 - A Study of CNTO 136 (Sirukumab) Administered Subcutaneously in Japanese Patients With Active Rheumatoid Arthritis Unresponsive to Methotrexate or Sulfasalazine
18. NCT02019472 - CNTO136ARA3005 - A Multicenter, Randomized, Double-blind, Parallel Group Study of Sirukumab Monotherapy Compared With HUMIRA® Monotherapy Administered Subcutaneously, in Subjects With Active Rheumatoid Arthritis
19. NCT01645280 - CNTO1275ARA2001 - A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Study Evaluating the Efficacy and Safety of Ustekinumab (STELARA®) and CNTO 1959 Administered Subcutaneously in Subjects With Active Rheumatoid Arthritis Despite Concomitant Methotrexate Therapy

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

Research Proposal

Project Title

A meta-analysis to assess relationships between patient demographics and response to antibody-based treatment in rheumatoid arthritis patients

Narrative Summary:

Rheumatoid arthritis (RA) is an autoimmune disease which has a significantly higher incidence in women than men. Inhibitory or neutralising antibodies against pro-inflammatory factors such as tumour necrosis factor alpha (TNF-?), interleukin (IL) 6, 12 or 23 can dampen hyperactive immune response. While activation of these proinflammatory factors is a common symptom in RA, basal patient characteristics before/during treatment as well as several external factors can influence response to antibodies. The objective of this study is to identify patient characteristics which can lead to heterogeneity in response to a therapy and guide drug selection in a personalised manner.

Scientific Abstract:

Background:
Rheumatoid arthritis (RA) is a long-term autoimmune disease which is characterised by swelling, stiffness, and pain in the joints. The cause of this disease where immune cells attack one's own cells is not well known. Epidemiological studies has clearly shown a gender bias with women being three-four times more likely to develop RA in their lifetime[1]. Since the cause of RA is not clear, the treatment is focussed on managing symptoms. Most anti-inflammatory drugs reduce the sensation of pain but do not modify the disease itself. Disease modifying therapies aim to dampen the overactivated immune system and are categorised as immunosuppressants, the most prescribed immunosuppressant being methotrexate (MTX). Advances in monoclonal antibodies (mAbs) and chimeric mAbs has broadened the druggable targets and this has led to development of anti tumour necrosis factor alpha (TNF-?) (e.g., Adalimumab [2–4], Golimumab [5–7], infliximab [8,9]), anti interlukin 6 (IL6) (e.g., Sirukumamb [10–13]), and anti-IL23 (e.g., guselkumab [14]) and dual IL12/IL23 targeting antibodies (e.g., ustekinumab [14]) which have completed several phase II/III clinical trials as primary therapy or as a secondary therapy in patients who have already received/are receiving disease-modifying antirheumatic drug (DMARD) therapy.
Since, the triggers/causes of disease are not clear, more epidemiological studies are necessary to understand the role of various factors including environmental as well as genetic risk factors. Additionally, the differences in response to therapies could potentially result in molecular differences in the disease pathology.

Objective: The main objective of this study is to pore into the rich randomised clinical trial (RCT) data and identify potential correlations between patient demographics as well as environmental factors and effectiveness of different RA treatments.

Study Design: Meta-anlysis of published RCT

Participants: Adults (>18 years) with Rheumatoid arthritis

Primary and Secondary Outcome Measure(s): Primary: ACR20, Secondary: ACR50

Statistical Analysis: A suite of statistical approaches including network-based correlation analyses and logistical regression analyses and other machine learning algorithms will be used to assess the potential risk factors associated with poor response to therapies. A meta-analysis of data will be performed with random effect model to compare different therapies. More details are provided in the statistical analysis plan section of this data request form.

Brief Project Background and Statement of Project Significance:

This project is aimed to identify associations and prognostic markers for treatment with antibody-based treatments to determine the efficacy of different treatments against rheumatoid arthritis. We are also interested to assess any demographics factors that might explain differences in efficacy and safety profile in rheumatoid arthritis patients. We hope that this analysis will lead to new insights about the effect of the arthritis treatment and their dependence on patient characteristics and has the potential to maximise benefit of this drug for rheumatoid arthritis in the future. Recent work has compared different antibodies using network-based approach [15]. Our work will aim to identify any associations between patient demographics and outcome when treated with different antibodies.

Specific Aims of the Project:

Hypotheses:
1) The level of activation of pro-inflammatory factors varies across patients and hence, the response to the same dose of an antibody may be difference across patients with RA

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

2) Antibodies targeting different pro-inflammatory factors in the same pathway may have different distribution profile and ability to neutralise or inhibit the activity of aberrant immune activation and off-target interactions. This can influence the response and safety and therefore, some patients subgroups may have a better response to one treatment vs the other
3) By combining multiple clinical trials, we can potentially do these comparisons and identify relationships between the response to a therapy as well as safety profile and patient characteristics as well as mode of delivery
Aims and objectives:
1) To assess whether factors such as gender, age, location, BMI, disease duration, prior treatment, ethnicity, smoking, mode of delivery, etc. impacts the response to antibody-based therapies
2) Identify potential prognostic markers which can enable choosing the right antibody-based therapy and pave the way for more personalised medicine.

What is your 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

New research question to examine treatment safety

Confirm or validate previously conducted research on treatment effectiveness

Confirm or validate previously conducted research on treatment safety

Participant-level data meta-analysis

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

Develop or refine statistical methods

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:

We will be conducting analysis on trials provided on the Yoda website (no external sources beyond Yoda). Any other aggregate data on the trials listed on the Yoda website will be obtained from links on each Yoda trial page, e.g. from ClinicalTrials.gov, and trial-associated publications.
Inclusion criteria:
- We will be conducting our analyses on randomly controlled trials, controlled with a placebo group.
- Age of patients >= 18 years
- Patients have rheumatoid arthritis
Exclusion criteria:
- Trials with no subgroup details on age, gender, country, etc. will be excluded from subgroup level analyses

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

Primary: ACR20 – defined as a >20% improvement in the number of tender and number of swollen joints and in 3 of the following 5 criteria: patient global assessment, physician global assessment, functional ability measure, visual analog pain scale and erythrocyte sedimentation rate or C-reactive protein (CRP)
Secondary: ACR50 (as above but >50%)

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

- Age: <50, ?50 years
- Gender: Woman or Man
- Ethnicity: Depends on the dataset
- Disease duration: Depends on the dataset
- Rheumatoid factor (RF) positivity or negativity
- BMI: <18.5, 18.5-24.9, 25-29.9, 30-34.9, >35 (Depends on the dataset)
- Physical activity: <30 min/week, >30 min/week (Depends on the dataset)

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

Previous / current other drugs used. E.g. MTX, anti TNF alpha, etc.

Statistical Analysis Plan:

- Descriptive statistics will be used to assess bivariate relationships between single independent variable (age, gender, etc.) and primary/secondary outcome. Log ratios will be evaluated using logistical regression analyses
- Multivariable analyses (classification models, analysis of variance (ANOVA), clustering, etc.) will be performed by combining multiple independent variables.
- A random effect models will be used to conduct meta-analysis19 as the objective is to potentially use the results beyond the existing clinical trials
- When conducting meta-analysis a three stage approach will be used:
o Cochrane risk-of-bias tool: ROB216 will be used to identify any discrepancies or biases in the clinical trials. Although studies will not be excluding despite having high risk of bias, but these will be highlighted when discussing the analyses and methods to account for bias will be applied if time permits17,18.
o A summary statistic will be calculated for each study, to describe the observed intervention effect in the same way for every study. Since our outcomes are ACR20 and ACR50 (discrete variables), risk ratio will be used for analysis.
o A summary (combined) intervention effect estimate will be calculated as a weighted average of the intervention effects estimated in the individual studies.
Software Used:
Python
Project Timeline:

Data gathering and method selection: October-November 2022
Data analysis and interpretation: November 2022-July 2023
Data summary, visualisation and report submission: Sept. 2023

Dissemination Plan:

The findings will be discussed within the department as well as a project report will be submitted at the end of the project. Additionally, any novel insights will be shared with the wider scientific community in the form of a journal publication and by presentations or posters in academic conferences.

Bibliography:

References
1. Ngo, S. T.; Steyn, F. J.; McCombe, P. A. Gender Differences in Autoimmune Disease. Front. Neuroendocrinol. 2014, 35 (3), 347–369. https://doi.org/10.1016/j.yfrne.2014.04.004.
2. Weinblatt, M. E.; Keystone, E. C.; Furst, D. E.; Moreland, L. W.; Weisman, M. H.; Birbara, C. A.; Teoh, L. A.; Fischkoff, S. A.; Chartash, E. K. Adalimumab, a Fully Human Anti-Tumor Necrosis Factor ? Monoclonal Antibody, for the Treatment of Rheumatoid Arthritis in Patients Taking Concomitant Methotrexate: The ARMADA Trial. Arthritis Rheum. 2003, 48 (1), 35–45. https://doi.org/10.1002/art.10697.
3. Bartelds, G. M.; Wijbrandts, C. A.; Nurmohamed, M. T.; Stapel, S.; Lems, W. F.; Aarden, L.; Dijkmans, B. A. C.; Tak, P. P.; Wolbink, G. J. Clinical Response to Adalimumab: Relationship to Anti-Adalimumab Antibodies and Serum Adalimumab Concentrations in Rheumatoid Arthritis. Ann. Rheum. Dis. 2007, 66 (7), 921–926.

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

https://doi.org/10.1136/ard.2006.065615.
4. Lovell, D. J.; Ruperto, N.; Goodman, S.; Reiff, A.; Jung, L.; Jarosova, K.; Nemcova, D.; Mouy, R.; Sandborg, C.; Bohnsack, J.; Elewaut, D.; Foeldvari, I.; Gerloni, V.; Rovensky, J.; Minden, K.; Vehe, R. K.; Weiner, L. W.; Horneff, G.; Huppertz, H.-I.; Olson, N. Y.; Medich, J. R.; Carcereri-De-Prati, R.; McIlraith, M. J.; Giannini, E. H.; Martini, A. Adalimumab with or without Methotrexate in Juvenile Rheumatoid Arthritis. N. Engl. J. Med. 2008, 359 (8), 810–820. https://doi.org/10.1056/nejmoa0706290.
5. Keystone, E. C.; Genovese, M. C.; Klareskog, L.; Hsia, E. C.; Hall, S. T.; Miranda, P. C.; Pazdur, J.; Bae, S. C.; Palmer, W.; Zrubek, J.; Wiekowski, M.; Visvanathan, S.; Wu, Z.; Rahman, M. U. Golimumab, a Human Antibody to Tumour Necrosis Factor ? given by Monthly Subcutaneous Injections, in Active Rheumatoid Arthritis despite Methotrexate Therapy: The GO-FORWARD Study. Ann. Rheum. Dis. 2009, 68 (6), 789–796. https://doi.org/10.1136/ard.2008.099010.
6. Smolen, J. S.; Kay, J.; Doyle, M. K.; Landewé, R.; Matteson, E. L.; Wollenhaupt, J.; Gaylis, N.; Murphy, F. T.; Neal, J. S.; Zhou, Y.; Visvanathan, S.; Hsia, E. C.; Rahman, M. U. Golimumab in Patients with Active Rheumatoid Arthritis after Treatment with Tumour Necrosis Factor ? Inhibitors (GO-AFTER Study): A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase III Trial. Lancet 2009, 374 (9685), 210–221. https://doi.org/10.1016/S0140-6736(09)60506-7.
7. Singh, J. A.; Noorbaloochi, S.; Singh, G. Golimumab for Rheumatoid Arthritis: A Systematic Review. J. Rheumatol. 2010, 37 (6), 1096–1104. https://doi.org/10.3899/jrheum.091466.
8. Wolfe, F.; Michaud, K. The Effect of Methotrexate and Anti-Tumor Necrosis Factor Therapy on the Risk of Lymphoma in Rheumatoid Arthritis in 19,562 Patients during 89,710 Person-Years of Observation. Arthritis Rheum. 2007, 56 (5), 1433–1439. https://doi.org/10.1002/art.22579.
9. St.Clair, E. W.; Van Der Heijde, D. M. F. M.; Smolen, J. S.; Maini, R. N.; Bathon, J. M.; Emery, P.; Keystone, E.; Schiff, M.; Kalden, J. R.; Wang, B.; DeWoody, K.; Weiss, R.; Baker, D. Combination of Infliximab and Methotrexate Therapy for Early Rheumatoid Arthritis: A Randomized, Controlled Trial. Arthritis Rheum. 2004, 50 (11), 3432–3443. https://doi.org/10.1002/art.20568.
10. Hu, C.; Xu, Y.; Zhuang, Y.; Hsu, B.; Sharma, A.; Xu, Z.; Zhang, L.; Zhou, H. Joint Longitudinal Model Development: Application to Exposure–Response Modeling of ACR and DAS Scores in Rheumatoid Arthritis Patients Treated with Sirukumab. J. Pharmacokinet. Pharmacodyn. 2018, 45 (5), 679–691. https://doi.org/10.1007/s10928-018-9598-5.
11. Takeuchi, T.; Thorne, C.; Karpouzas, G.; Sheng, S.; Xu, W.; Rao, R.; Fei, K.; Hsu, B.; Tak, P. P. Sirukumab for Rheumatoid Arthritis: The Phase III SIRROUND-D Study. Ann. Rheum. Dis. 2017, 76 (12), 2001–2008. https://doi.org/10.1136/annrheumdis-2017-211328.
12. Aletaha, D.; Bingham, C. O.; Tanaka, Y.; Agarwal, P.; Kurrasch, R.; Tak, P. P.; Popik, S. Efficacy and Safety of Sirukumab in Patients with Active Rheumatoid Arthritis Refractory to Anti-TNF Therapy (SIRROUND-T): A Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Multinational, Phase 3 Study. Lancet 2017, 389 (10075), 1206–1217. https://doi.org/10.1016/S0140-6736(17)30401-4.
13. Aletaha, D.; Bingham, C. O.; Karpouzas, G. A.; Takeuchi, T.; Thorne, C.; Bili, A.; Agarwal, P.; Hsu, B.; Rao, R.; Brown, K.; Tanaka, Y. Long-Term Safety and Efficacy of Sirukumab for Patients with Rheumatoid Arthritis Who Previously Received Sirukumab in Randomised Controlled Trials (SIRROUND-LTE). RMD Open 2021, 7 (1). https://doi.org/10.1136/rmdopen-2020-001465.
14. Smolen, J. S.; Agarwal, S. K.; Ilivanova, E.; Xu, X. L.; Miao, Y.; Zhuang, Y.; Nnane, I.; Radziszewski, W.; Greenspan, A.; Beutler, A.; Baker, D. A Randomised Phase II Study Evaluating the Efficacy and Safety of Subcutaneously Administered Ustekinumab and Guselkumab in Patients with Active Rheumatoid Arthritis despite Treatment with Methotrexate. Ann. Rheum. Dis. 2017, 76 (5), 831–839. https://doi.org/10.1136/annrheumdis-2016-209831.
15. Janke, K.; Biester, K.; Krause, D.; Richter, B.; Schürmann, C.; Hirsch, K.; Hörn, H.; Kerekes, M. F.; Kohlepp, P.; Wieseler, B. 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, 1–11. https://doi.org/10.1136/bmj.m2288.
16. Higgins, J. P. T.; Altman, D. G.; Gøtzsche, P. C.; Jüni, P.; Moher, D.; Oxman, A. D.; Savovi?, J.; Schulz, K. F.; Weeks, L.; Sterne, J. A. C. The Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomised Trials. BMJ 2011, 343 (7829), 1–9. https://doi.org/10.1136/bmj.d5928.
17. Thompson, S.; Ekelund, U.; Jebb, S.; Lindroos, A. K.; Mander, A.; Sharp, S.; Turner, R.; Wilks, D. A Proposed Method of Bias Adjustment for Meta-Analyses of Published Observational Studies. Int. J. Epidemiol. 2011, 40 (3), 765–777. https://doi.org/10.1093/ije/dyq248.
18. Doi, S. A. R.; Thalib, L. A Quality-Effects Model for Meta-Analysis. Epidemiology 2008, 19 (1), 94–100. https://doi.org/10.1097/EDE.0b013e31815c24e7.
19. Tufanaru, C.; Munn, Z.; Stephenson, M.; Aromataris, E. Fixed or Random Effects Meta-Analysis? Common Methodological Issues in Systematic Reviews of Effectiveness. Int. J. Evid. Based. Healthc. 2015, 13 (3), 196–207.

https://doi.org/10.1097/XEB.0000000000000065.