TRAM MB-PhD Project Summary

(The completed form should not exceed 2 pages)

PhD project Title
Characterising treatment strategies and health outcomes for conventional and biologic disease modifying anti-rheumatic drugs (DMARDs) used in immune-mediated inflammatory diseases

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Background

Immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis and systemic lupus erythematosus, are clinically diverse medical conditions characterised by abnormal functioning of the body's immune response which leads to acute or chronic inflammation. IMIDs can cause chronic pain, lead to irreversible joint (e.g. bone erosion) and organ damage, and are associated with several complications, including cardiovascular disease [1].

Therapeutic options for IMIDs include non-steroidal anti-inflammatory drugs (NSAIDs), and immunosuppressive therapies, comprising glucocorticoids, conventional disease modifying anti-rheumatic drugs (cDMARDs), such as methotrexate, and over the last two decades biologic and targeted synthetic medicines (b/tsDMARDs) such as TNF inhibitors and JAK inhibitors. The latter class of medicines work by targeting specific proteins or cells of the immune system to help reduce the amount of inflammation and its damaging effects on tissues and organs.

While data from randomised controlled trials (RCTs) suggest that these medicines are safe and effective, there remain unanswered questions. Data on unexpected safety signals and on the generalisability of the RCT's findings to populations underrepresented in RCTs (those aged 75 or over, with comorbidities, diverse ethnic backgrounds, pregnant women) and over a longer time-horizon than the RCT's follow up are lacking, especially for newer treatments [2].

Furthermore, while b/tsDMARDs have greatly improved the outlook for people diagnosed with IMIDs, all classes of drugs have a substantial rate of insufficient response. About a third of patients started on b/tsDMARDs will respond well to medications. Two thirds will have a partial response, and about 6-10% of patients will not respond to treatment at all. Therefore, a large proportion of patients will try several medications before finding the treatment that works best.

In this project will use electronic health record data from a newly established national rheumatology linkage study to assess the effect of drug exposure on health outcomes and to study natural history of disease and drug trajectories in IMIDs. In this large-scale cohort we have linked data on prescriptions of b/tsDMARDs with health outcomes (hospital admissions, cancer registrations, death registry), prescriptions from primary care, radiological imaging reports and lab

test results for all people seen in rheumatology clinics in Scotland. Pseudonymised linked data will be analysed within the National Safe Haven of Public Health Scotland.

Aims

1) To inform research questions about the efficacy and safety of medicines used in day-to-day rheumatology practice to treat people with IMIDs.
2) To characterise treatment trajectories and assess if clinical factors, disease symptoms or patient characteristics, available prior to treatment, can predict treatment response in IMIDs.

Training and experience provided

1) Learning to work with electronic health care records, including understanding clinical coding systems, such as the International Classification of Diseases (ICD), data governance and data protection principles, and working within the National Safe Haven computing environment.
2) Statistical methods for case/control and time-to-event analyses and for training and evaluating the performance of clinical prediction models.
3) Learning the R statistical programming language, working with relational databases, such as MySQL, and using tools for reproducible research, including Rmarkdown and version control (Git).
4) Working with academic rheumatologists and understanding the current clinical practice in the management of IMIDs.
5) Interpretation of various imaging techniques and blood tests used in rheumatology.

Expected outcomes

This research can address safety concerns for newer medications where rare but important side effects could have been missed by clinical trials and for patient subgroups that are typically excluded in trials (e.g. pregnant women, aged 75+).
This research can help identify who is more likely to develop long-term disability or loss of function and provide data to inform treatment strategies.
Findings from this research can be used to update prescribing recommendations and guidelines.

References

[1] McInnes IB, Gravallese EM. Immune-mediated inflammatory disease therapeutics: past, present and future. Nat Rev Immunol. 2021;21(10):680-686. doi:10.1038/s41577-021-00603-1

[2] Strait A, Castillo F, Choden S, et al. Demographic Characteristics of Participants in Rheumatoid Arthritis Randomized Clinical Trials. JAMA Netw Open. 2019;2(11):e1914745. doi:10.1001/jamanetworkopen.2019.14745