Safety of urate lowering therapy for gout in the UK and Taiwan: A population-based comparative cohort study using the CPRD (n=14m) and NHI (n=23m) databases

Section 1 – Project Details:

Maximum 800 words using the following headings

Rationale:

Gout is the commonest inflammatory arthritis affecting one in 40 people in the UK general population\(^1\). The incidence of gout increases 1.5% each year and the prevalence increases 4% each year, whereas the management of the disease remains consistently poor\(^1\). We have recently confirmed in an initial proof of concept study\(^2\) and subsequent two year community-based randomised controlled trial that appropriate use of urate lowering therapy can improve patient-centred outcomes. However, there are many barriers to care due to lack of understanding of the disease and incorrect illness perceptions in patients and practitioners\(^3\). Also many practitioners are wary of the safety of available urate lowering drugs (ULDs). “Allopurinol Hypersensitivity Syndrome” (AHS), presenting clinically as Drug Rash Eosinophilia and Systemic upset Syndrome (DRESS), Steven Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN), sometimes with acute renal failure and liver function impairment are indeed life-threatening. However, apart from case reports and relatively small surveys of people with DRESS, SJS or TEN, there are relatively little data concerning the incidence and risk factors of clinically important adverse events associated with ULDs. This study aims to examine ULD safety using post-marketing data from the UK Clinical Practice Data-Link (CPRD, 15 million), and Taiwan National Health Insurance (NHI, 23 million) Database. The reason to choose these two databases is because AHS is genetic predisposed by possession of HLA-B5801, which is more commonly present in Chinese and Asian people than in Caucasians\(^4,5\) and also because allopurinol is most commonly used in the UK whereas benzbromarone is most commonly prescribed in Taiwan.

Aims and methodology:

Aims:

To investigate the safety of commonly used ULDs in two general populations (Chinese and British)

Methodology

The following studies will be undertaken in this PhD programme:

1. A systematic review of randomised controlled trials (RCTs), cohort studies, case control studies and cross sectional studies to examine the safety of ULDs globally
2. A network meta-analysis to examine the relative safety between different ULDs
3. A cohort study to compare users with non-users of ULDs for incidence of adverse events in the UK and Taiwan
4. A comparison between Chinese and British on the use of different ULDs and their associated adverse events

For studies 1 and 2, we will include studies with the following PICOs (participants, interventions, comparators and outcomes)
Participants: people with gout
Interventions: ULDs including allopurinol, febuxostat, benzbromarone, probenecid and sulphinpyrazone
Comparators: placebo, no treatment control, or another ULD
Outcomes: adverse events categorised as any and by system (skin, liver, renal, cardiovascular etc). Severe systemic adverse events (AHS, DRESS), SJS or TEN, and liver or renal failures) will be summarised specifically.

Systematic literature search will be undertaken using Medline, Embase and Web of Sciences. RCTs, cohort studies, case control studies and cross-sectional studies fulfilling the above PICOs will be included. Relative risk (RR), odds ratio (OR), or hazard ratio (HR) will be calculated. They will be pooled according to ULD. Heterogeneity and publication bias will be examined. Evidence from RCTs and observational studies will be summarised separately. Network meta-analysis will be conducted to estimate the relative safety between ULDs.

For studies 3 and 4 we will undertake two cohort studies, one in Taiwan and the other in the UK. Incident gout patients (first diagnosis in the database) will be identified from each country with at least a 10 year period available to follow up. First ULD prescription date will be used as the index date to follow-up. Number of prescriptions will be documented thereafter and cumulated defined daily dose (cDDD) will be calculated. Each incidence gout case will be matched with a non-gout control by age, gender and practice. They will be followed up from the same index date until the events of interest, end of follow-up, removal or death whichever comes first. Survival analysis will be used to determine the time to event outcome. Kaplan Meier survival curve will be given and COX proportional hazard model will be used to adjust for confounding. To minimise the survival bias, landmark analysis will be used. Comparison will be made between the two populations in terms of use of ULDs and major adverse events. Nested case control studies will be conducted to explore the risk factors associated with the adverse events.

Benefits and suitability as a PhD project:

This PhD programme will permit the candidate to learn how to conduct: [1] systematic review; [2] network meta-analysis; and [3] big data pharmacoepidemiology study. Throughout this programme the candidate will learn the differences between trials and observational studies. As no recruitment is required, the programme can be completed within 3 years. It is likely to lead to several 3* or 4* publications such as references 1 and 3.

Key References: please see the end of this proposal

Section 2 – Training Provision:

Maximum of 250 words. Please detail the training provision that will be made available to the student.

WZ is an international expert in systematic review and meta-analysis. He is an epidemiologist with experience in both epidemiology (cross-sectional, case control and cohort studies) and big data (e.g., CPRD and NHI). MD is an international gout expert with experience in clinical trials, evidence based medicine and epidemiology. AA is a rheumatologist with special interests in gout and experience in CPRD.
The international collaborator Dr Changfu Kuo is the Head of the Rheumatology and the Director of Centre for Big Data Analytics and Statistics in Taiwan. He has published over 20 research papers in CPRD and NHI and has become an international leading expert in gout and big data epidemiology.

The team has obtained fundings to access both databases. The team has been supervising 3 PhDs, two of whom have been successfully awarded using the CPRD and NHI.

The candidate will be trained by the introduction course provided by the MHRA for CPRD, and by Dr Changfu Kuo’s Department for NHI. S/he will then be trained by the statistics/epidemiology courses provided by the Division of Public Health and Epidemiology. The candidate will attend the Graduate School and N-trains courses for systematic review/meta-analysis and network meta-analysis etc. In addition, regular supervision meeting (every fortnight) will be conducted throughout this PhD programme to ensure sufficient training and outputs.

Reference List


