The use of real-world data to address questions of patient safety

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Abstract
Registries were established to evaluate the risk of adverse events including infection and malignancy in patients taking biologic therapies, which may be missed in trials due to their shorter durations and homogeneous samples. They are a relatively inexpensive approach that achieves high statistical power, allows direct comparability, and offers a level of detail on adverse events not possible with trial data. Registries have been central in clarifying the risk of infection and malignancy with anti-TNF therapy despite the limitations of selection and channelling bias, incomplete case capture, unmeasured confounding, and the inability to infer causality. Routinely collected data from electronic health records and national audits offer alternative real world resources, further assisting patients and clinicians in understanding the risks of biologic therapy choices.

Key Words: registries, biologic therapy, rheumatoid arthritis, real world data, adverse events.

Key messages:
1. Registries are an inexpensive approach with statistical power and duration of follow up not achievable with traditional trial based studies;
2. Registries have been essential in establishing the long term risk of infection and malignancy with biologic therapies;
3. Routinely collected electronic health record and national audit data offer a further real world data resource to complement registries.

Introduction
Targeted therapies have revolutionised the management of inflammatory arthritis, with vast improvement in disease outcomes. In the late 1990’s as anti-tumour necrosis factor (anti-TNF) was first launched as a therapy in rheumatoid arthritis (RA), many questions arose regarding safety. It was felt that traditional methods of post marketing surveillance, such as spontaneous pharmacovigilance or phase IV industry sponsored trials would be inadequate to fully evaluate the safety concerns of a new class of treatment. Contemporary to the early years of biologic therapy were the emerging safety concerns of Cox-2 selective drugs and thialidozinediones in diabetes (1, 2). The last two decades have witnessed not only a series of landmark changes in treatment paradigms, but also dramatic improvements in how we collect, analyse and interpret safety data collected in the ‘real-world’ setting.

The concept of the real-world is of course slightly artificial, as even clinical trials technically take place in the real-world. However, clinical trials fall short in their ability to robustly study adverse outcomes:
 Trials are powered to determine efficacy which generally requires far smaller numbers than would be required to compare safety outcomes;

 Trials are of short duration, typically 12 months or less, which is inadequate for outcomes such as cancer which have a lagged exposure risk;

 Trials self-select for patients who are fit to participate in research, often recruiting a healthier cohort that is not entirely representative of the patient population as a whole.

Alternative solutions evolved in response to these limitations, initially in the form of drug registers, and subsequently by the use of routinely collected information from administrative databases and national clinical audits. The purpose of this review is to consider the major strengths and weaknesses of these types of study, using some of the analyses of infection risk and cancer risk as exemplars.

Strengths of registries:

1. Statistical power

Registries have the capability to collect data on a vastly greater number of subjects than clinical trials. An excellent example of the benefit of sample size is in the field of infection risk. There is an inherently plausible link between immunosuppression and infection risk. Quantifying the risk and comparing across different treatment strategies inevitably attracts the attention of both physicians and patients. Before considering the evidence from registries, it is relevant to review the data from the clinical trials. A meta-analysis of randomised controlled trials (RCTs) evaluating the risk of infection with anti-TNF reported the odds of serious infection as 1.2 (95% CI 0.89 to 1.63) based upon 6347 patients with 5830 patient years follow-up (3). In comparison, The British Society for Rheumatology Biologics Register (BSRBR-RA) reported the hazard ratio (HR) of serious infection in patients receiving anti-TNF as 1.2 (95% CI 1.1 to 1.5), based upon 15,396 patients with 45,489 patient years follow-up (4). A particularly striking observation regarding the BSRBR data is the enormous patient-years collated compared to pooled trial data, leading to the finding of a significant association between anti-TNF and serious infection.

This volume of follow up has enabled the BSRBR-RA data to be used to study very rare outcomes, including opportunistic infections across biologic drug classes. In one analysis, 19,282 patients with 106,347 years of follow-up were studied; 142 non-TB opportunistic events were identified,
representing an annual risk of approximately 1/1000. The overall incidence of opportunistic infection was not significantly different between the different drug classes; however, individual infections did differ with *Pneumocystis jirovecii* infection observed more frequent in rituximab compared with anti-TNF users (5).

2. Identifying detailed clinical information about adverse events

The German Register (RABBIT) undertook a particularly valuable analysis exploring lower gastrointestinal perforation risk – an observation suggested by data from randomised trials (6). The RABBIT register demonstrated a significantly increased crude incidence rate amongst tocilizumab users (2.7/1000 person-years) compared with other treatments (0.2 to 0.6/1000 person-years). The adjusted HR compared to conventional synthetic disease-modifying anti-rheumatic drugs was 4.5 (95% CI 2.0 to 10.0), in anti-TNF 1.0 (0.5 to 2.3), and in other biologic DMARDs 0.3 (0.1 to 1.4). The register was able to examine more details of individual cases, identifying that patients treated with tocilizumab presented without typical symptoms of perforation (acute abdomen, severe pain), with reduced biomarkers of infection (only one patient had highly elevated C reactive protein), and a higher 30-day mortality (7).

3. Direct rather than indirect comparisons

A Cochrane systematic review and network meta-analysis included 163 clinical trials with 50,010 participants and 46 extension studies with 11,954 participants (8). The median duration of each trial was six months, and 13 months for the extension studies. Indirect comparisons revealed certolizumab pegol was associated with a statistically higher odds of serious infections compared with abatacept, adalimumab, etanercept, golimumab, and rituximab. The Cochrane study was a landmark publication. However, an important limitation should be considered. A network meta-analysis relies on indirect comparisons between the drugs by utilising a common comparator. Differences in study design of each trial can introduce error into this comparison. This is not the case with registries in which for each drug the same methodology is used to detect and report on adverse events.

The BSRBR-RA has studied comparative risks of infection across biologic agents (9). The analysis included 19,282 patients with 46,771 years of follow-up. The incidence of serious infection was 5.5 cases per 100 patient years for the entire cohort (95% CI 5.3 to 5.7). Compared with etanercept, tocilizumab had a higher risk (HR 1.2, 95% CI 1.0 to 1.5) and certolizumab pegol a lower risk of serious
infection (HR 0.8, 95% CI 0.6 to 1.0). This is in direct contrast to the findings from the Cochrane review. The lower risk with certolizumab pegol was no longer significant in sensitivity analyses, and the authors suggested that unmeasured confounding may have accounted for the observed difference. From the BSRBR-RA results, it would be wrong to conclude certolizumab pegol has a lower infection risk than other biologics; however, the risk does not appear to be as high as previously suggested.

4. Capturing disease severity

The United States based CORRONA RA registry has investigated the impact of sustained remission on risk of serious adverse events. In an analysis of 12,329 patients (27% in sustained remission), the lowest incidence rate of serious adverse events was seen in patients in remission (1.03, 95% CI 0.85 to 1.26) (10). The study showed that even low disease activity was associated with serious infection, compared to remission. Compared to patients with sustained remission, the serious infection rate was 70% higher in patients with low disease activity (adjusted incident risk ratio (IRR) 1.69 (95% CI 1.32 to 2.15))

5. The dogged perseverance of researchers

Given the role of the immune system in cancer surveillance, it has been a long held concern that anti-TNF therapy may predispose to malignancy. Given that RA itself is associated with an increased lymphoma risk (11), the task of identifying if biologics independently increase the risk of cancer is challenging. A number of analyses using registry data were performed to answer this crucial question.

Mercer et al assessed the risk of solid organ cancers by linking the BSRBR-RA with national cancer registries for 3249 patients commenced on anti-TNF therapy with no prior history of malignancy. There were 427 solid cancers in 52,549 patient years in those treated with anti-TNF, compared to 136 cancers in 11,672 patient years in those treated with conventional disease modifying anti rheumatic drugs (DMARDs). After adjusting for demographics, anti-TNF therapy had a non-significant HR of 0.83 (95% CI 0.64 to 1.07) for solid organ cancer compared to conventional DMARDs (12). In addition, mortality in those diagnosed with a solid cancer was similar between the anti-TNF and conventional DMARD treated patients. Following on from this the BSRBR-RA was utilised to assess the risk of incident cancer in patients with a prior malignancy receiving anti-TNF. The age and gender adjusted HR was 0.55 (95% CI 0.35 to 0.86) in those receiving anti-TNF compared to conventional DMARDs, suggesting anti-TNF reduces the risk of recurrent malignancy (13). Finally, a collaborative project
including 12 European biologics registries compared the distribution of lymphoma in 124,997 patients receiving anti-TNF therapy or conventional DMARDs. They found no difference in lymphoma subtype distributions in RA treated with anti-TNF compared with bionaive patients (14).

Anti-TNF therapy is now the most extensively studied of the biological therapies for an association with malignancy, thanks to a large body of work utilising registry data. This allows us to say with confidence that there is no association between anti-TNF therapy and solid organ malignancy, including patients with a past history of cancer. Those who develop cancer while on therapy fare no worse, and it is likely that disease activity is the driver of malignancy risk in RA.

**Weakness of registries**

1. **Channelling bias and selection bias**

Registries are by their nature observational studies, where recording of information tends to be carried out by clinicians rather than investigators. The limitations of registry data should be carefully considered when making inferences.

Channelling bias refers to when heterogeneity in the population studied impacts on treatment decisions. An example of this comes from two studies investigating the risk of lymphoma with anti-TNF therapy using Swedish registry data. The first study ran from 1997 to 2002 and reported the risk of lymphoma in patients treated with anti-TNF as an IRR of 4.9 (95% CI 0.9 to 26.2) compared to a community based cohort treated with conventional DMARDs (15). The second study ran from 1999 to 2004 and reported a lower IRR of 0.8 (95% CI 0.4 to 1.4) compared to an early RA comparator cohort (16). Although non-significant, the IRR estimates are vastly different. Upon a closer examination of the data, the rates of lymphoma in the anti-TNF treated groups vary widely, with the later study having nine cases per 10,000 patient years compared to 31 cases per 10,000 patient years in the earlier study. This could be explained by channelling by clinicians, where concern regarding lymphoma risk with anti-TNF increased with time, leading to more pre-treatment screening and a reduction in the number of high risk patients being offered anti-TNF therapy in the later study (17).

Selection bias is also seen in the comparator populations from these two studies. The first study used a community-based RA cohort as the comparator. The second study has two comparator groups: an early RA cohort, and an inpatient RA cohort. An inpatient cohort is likely to have a more severe RA
phenotype and comorbidities than a community-based cohort, which likely influenced the rate of lymphoma.

Depending on the country of study, there may be drug selection bias due to restrictions on prescribing. An important observation of the BSRBR-RA data is that abatacept is notably absent from the results. Abatacept was never adopted on the UK register because it was very late to receive funding approval in the National Health Service.

Recruitment of patients to registries requires the time and goodwill of clinicians. Rheumatology departments conducting research will likely put more emphasis on including patients in registries and have dedicated research staff to assist in doing so. This may skew cohorts, whereby they are more a reflection of patients undergoing care at research orientated departments rather than the wider population. Over time, a greater understanding of the side effect profiles of anti-TNF and other biologics has likely led to increased clinician comfort with the risks of therapy and an overall increase in prescribing. This could contribute to a reduction in the recruitment of patients onto some, but not all drug registries. For example, the RABBIT register in Germany has maintained a constant rate of recruitment since inception, with the majority of patients enrolled from non-research orientated departments.

2. Incomplete capture of cases and missing data

Registries are susceptible to missing data and right censorship, where a patient no longer provides follow up data before the event of interest has occurred. This can particularly pose a problem when studying rare adverse events.

3. Unmeasured confounders

The choice of comparators in registers is crucial. The human mind is inherently influenced by what comparator we are presented with: this is a well-known cognitive bias, often termed anchoring. Pharmacoepidemiological studies do not escape this effect. Unlike a clinical trial, where patients are randomly allocated a treatment arm, drug registers accept patients into whichever arm their clinician has chosen. That clinical choice will have been influenced by innumerable characteristics: patient disease phenotype, comorbidity, clinician preference, drug costs. Any subsequent comparison must bear these differences in mind. Statistical modelling can address these differences when they are
known, but some degree of unmeasured confounding will inevitably remain. This does not diminish registry analyses but is vital to acknowledge when interpreting results. One strategy to overcome the issues of confounding has been to compare across biologic arms, as opposed to comparing biologic treated patients to conventional synthetic DMARD cohorts, although undoubtedly the decision of which biologic to prescribe is also influenced by patient and disease characteristics.

**Real World data- an alternative to registries**

The routine capture of data via electronic health records could in theory allow complete capture of data across a healthcare system, reducing selection bias and a resultant skewed cohort. An exemplar of this is healthcare insurance data in the United States, which was utilised to assess the risk of subsequent infections in patients who received biologic therapy after a serious infection requiring hospitalisation. They identified 10,183 patients with RA with 7807 person-years of exposure to biologic therapy. The risk of a subsequent serious infection was lower for both abatacept (HR 0.8, 95% CI 0.64 to 0.99) and etanercept (HR 0.83, 95% CI 0.72 to 0.96) users compared to those taking infliximab (18). In this case, the administrative dataset did not allow capture of disease activity scores, suggesting there may have been unmeasured confounding by disease severity, an important limitation.

A further example utilising health record data comes from a Korean study utilising national health insurance claims to assess factors associated with anti-TNF treatment duration in patients with RA (19). All new starters on anti-TNF over a one year period were identified, amounting to 388 patients, and the duration of treatment calculated using the time between first and last filled prescriptions over an 18 month period. Anti-TNF treatment persistence estimated via survival analysis was 61% at 18 months. This is consistent with findings from registry studies, portraying that routinely captured data can answer similar research questions without the onus on clinicians to recruit patients or collect data.

National audit schemes are another example where data can be routinely collected in clinical practice. The national early inflammatory arthritis audit (NEIAA) in England and Wales aims to capture information on routine care from diagnosis to one year follow up for patients with inflammatory arthritis. A strength of the project is that all rheumatology departments are contractually obliged to participate, which should in theory lead to complete case capture. In practice NEIAA relies on the good will of rheumatology clinicians to include their patients, with local departmental staffing levels and clinical workloads influencing participation rates. This potentially opens up national audit data to similar pitfalls as registries in terms of selection bias.
Whilst routinely collected datasets are expanding in availability, driven by the move to electronic data capture in the clinic, there is a tantalising interest in how such datasets will complement or even replace registries, although there is still a very long way to go before the latter option could be contemplated.

Conclusion
Registries have established themselves as essential resources for understanding post marketing surveillance, specifically referring to the safety of drug therapies. They are a cost-effective method of detecting rare serious adverse events that are often not identified in traditional trial based studies. They also allow high powered analyses with large sample sizes while avoiding the comparability pitfalls of network meta-analyses. In addition to the strengths of registries readers should be aware of their limitations, including the inability to infer causality and selection bias. Routinely collected healthcare datasets and national audits offer a future model of observational data to assist patients and clinicians in ascertaining the risk of therapy.

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