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BIOLOGIC REGISTERS IN RHEUMATOID ARTHRITIS: METHODOLOGICAL ASPECTS, CURRENT ROLE AND FUTURE APPLICATIONS

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[ABSTRACT]

The onset of the 21st century witnessed a biopharmaceutical revolution in the treatment of inflammatory rheumatic diseases. The fast evolving use of biologics highlighted the need for developing registers at national and international levels, with the aim of collecting long-term data on patient outcomes. Many biologic registers have now been in existence over 15 years contributing to a wealth of data and providing robust and reliable evidence on the use, effectiveness and safety of these biologics. The unavoidable challenges posed with the continuous introduction of new therapies such as the biosimilars and new class of janus kinases (JAK) inhibitors, especially with respect to understanding their safety in the longer term, highlights the importance of taking full advantage of learning from what has been published with respect to established biologic therapies. This article discusses the role of biologic registers in bridging the evidence gap with clinical trial data, focusing on methodological aspects of registers, unique features and challenges while considering their role going forward.

Introduction

The discovery and introduction of biologic treatment represents one of the most significant advances in the field of rheumatology. For rheumatoid arthritis (RA), biologics have transformed what was for many an incurable and devastating disease, into one that can be fully controlled.[1] Although multiple randomized clinical trials (RCTs) have demonstrated the efficacy of these therapies, the nature of RCT recruitment and short follow-up periods means that efficacy (i.e. how a drug performs under clinical trial conditions) may not directly translate into effectiveness (i.e. how it performs under standard clinical practice conditions). It was on this basis that within rheumatology, a number of biologic registers were established, such that further data from "real-world" practice could be captured and this evidence gap bridged. This Perspectives article discusses unique features, differences in methodological approaches and challenges in both the capture of and analysis of observational drug data when addressing questions around drug usage and effects in populations. It highlights key lessons learnt drawing examples from European registers while discussing potential future applications.

What Is A Biologics Register?

Rheumatology has a long tradition of observational research.[2] With the advent of biologic therapies for RA, many existing observational patient registers adapted their data collection to increase their focus on outcomes following exposure to biologic therapies. In many countries, however, new national biologics registers were established with the primary goal of studying treatment outcomes following biologics (see Figure 1 for examples in Europe).

In essence, a biologics register is an observational cohort study which includes capture of detailed data on exposure to biologic therapies, such as details of the underlying diagnosis, drug start and stop dates, as well as treatment outcomes. These outcomes might include disease activity, patient reported outcome measures (PROMS) such as the Health Assessment Questionnaire (HAQ), as well as the occurrence of new comorbidity or adverse events.

Although a majority of registers capture data across all of these areas, they do differ in their design. For example, in the UK and Germany, bespoke new cohort studies were established which recruited patients at the point of starting their first biologic. Both registers also aimed to recruit a cohort of patients receiving conventional standard DMARDs (csDMARDs) as a comparator. In the case of the UK, the BSRBR-RA did not set out from the start to capture data from all patients receiving a biologic, but instead to set recruitment targets and then stop recruitment when these targets were reached. This design differs from those based in countries which adapted or developed patient registers. Examples for the latter include Sweden (ARTIS), Denmark (DANBIO) or Switzerland (SCQM), whereby the capture of biologic data is embedded within a larger national patient register which aims to capture outcome data on all patients with RA, regardless of whether they receive biologic therapies.

Both approaches have their strengths and weaknesses but offer valuable sources of data on the effects of biologic therapies. Bespoke biologic registers have the

advantage of deep data capture particularly surrounding the occurrence and details of adverse events but due to the increased workload of capturing such data, are often not comprehensive in their patient capture. This is in contrast to patient care registers which can ensure capture of almost every patient with RA, and thus may have inbuilt comparison cohorts, but often must rely on external data sources, with variable outcome event details for capture of adverse events.

The large sample sizes, long follow-up and real-life populations included in biologics registers, contrast the relatively small and select, homogeneous RCT populations, enabling better external validity. Many registers also have the ability to link to a national death database, bio-repositories or have access to laboratory data, making them particularly suited to answering specific research questions.[3] Selected examples of established RA biologics registers, their purpose, design and unique features are shown in Table 1.

What Can We Learn About Biologic Therapies Using Biologics Registers?

RCTs remain the benchmark for measuring the efficacy of new therapies. However, they restrict patient inclusion, usually in an attempt to recruit a homogenous group of patients and thus are not always representative of the cohort of patients who will eventually go on to receive biologic therapies.[4,5] They are usually not powered to study the risk of less common outcomes, such as serious infection. As recruitment and follow-up are usually over a short period of time, latent effects, such as the risk of malignancy, may not be observed. Also, they cannot be used to comment on how clinical practice evolves over time. These are areas where data from registers can complement what information is obtained from clinical trials.

The Use of Biologics in Clinical Practice

Early reports from the German and Dutch registers found that a majority of patients who were receiving TNF inhibitors (TNFi) for RA would not have been eligible for participation in clinical trials.[4,5] This was explained by both a proportion of patients who were too ill or disabled to participate, but there was also a proportion of

patients whose disease was not active enough to be eligible. More recent data from the British register have shown that patients who start rituximab or tocilizumab as a first line biologic, as opposed to a TNFI, have higher frequencies of important co-morbidities such as prior cancer or interstitial lung disease, conditions which often preclude participation in RCTs.[6] A study from the Swiss Clinical Quality Management Programme for RA (SCQM-RA) register demonstrated that biologic DMARDs (bDMARDs) were more often prescribed as monotherapy to older patients with co-morbidity, lower BMI, longer disease duration, more previous bDMARDs and higher disease activity.[7] The study of register data over time has provided insights into secular changes in the use of biologics, demonstrating earlier use following fewer csDMARDs in patients with lesser amounts of disability and corticosteroid exposure.[8,9]

Biologic Treatment Effectiveness

It follows that if the patient populations receiving biologics differ from those in RCTs, it may be that the expected response rates to therapy also differ. In general, initial treatment responses are similar to those observed in clinical trials[10–12] but registers can go beyond treatment response and analyse long-term treatment persistence,[13–15] areas which have not been or can be explored in clinical trials. On average, 50% of patients have discontinued their first biologic by 5 years, either for ineffectiveness or adverse events.[13] Register data can also be used to compare between different biologic therapies. Data from the Danish DANBIO[11] and the Italian GISEA registers[16] suggested that infliximab was associated with the lowest rates of treatment response, disease remission and drug survival; the highest rates of treatment response and disease remission were observed with adalimumab; the longest drug survival rates with etanercept.[11]

The lack of head-to-head trials of the best second line treatments in RA also directed focus towards register data to compare outcomes among patients switching to different treatment options. The majority of evidence from register data, including the Spanish BIOBADASER[17] and Swedish STURE,[18] suggest that overall, response rates are lower and drug-retention rates decrease in patients receiving a subsequent

TNFi. Response to a second TNFi may differ according to the reason for initial TNFi treatment failure.[19] Swiss and British register data have shown rituximab to be more effective than switching to an alternative TNFi in RA patients with persistently active disease despite a TNFi, [20,21] a finding supported by a recent non-register observational study[22] as well as a large RCT.[23] These observations have formed a strong evidence-base for clinical decisions in routine clinical practice. Although the majority of data to date focus on TNFi, biologics registers have also already provided information on the use of newer biologics emerging over the course of the 21st century, including rituximab, abatacept and tocilizumab, [24–28]usually incorporated in existing registers or in newly-developed registers.

In addition to describing and comparing biologic treatment responses, registers have also better described the nature of patients who achieve a good response with TNFi. Factors which have been identified as being associated with response to treatment include younger age,[11] shorter disease duration,[29] better functional status at the start of therapy,[11,30,31] and non-smokers.[30,32–35] Furthermore, where studied, most registers have confirmed better treatment responses among patients who start TNFi alongside methotrexate, even in the setting of previous methotrexate failure.[10,13,31,36] However, across all of these examples, register data have shown that clinical data alone are not sufficient to predict which patients will have a good response, which has led to further biomarker studies in RA.[37]

Safety of Biologic Therapies

The very large sample sizes and longer follow-up periods of biologics registers have allowed an analysis of risk beyond that available from clinical trials. A majority of registers have confirmed a small but significant increase in the risk of serious infections early on in the course of TNFi therapy, which seems to decrease over time. [38,39, 24,40,41,42] Further exploration of the data held within the German RABBIT register, suggests this effect is due to both the depletion of patients at high risk of infection from the cohort, but also improvements in disease activity and lesser steroid use among those who do respond and stay on therapy, this reducing their individual infection risk. [43] In addition, observational drug registers have enabled the

study of potential benefits of treatment with respect to safety outcomes i.e. the association between TNFi and a reduced risk of cardiovascular events in RA patients.[44] A number of registers have also now published on the observed risk of cancer compared to patients receiving csDMARD therapies and have not confirmed an increased risk of solid organ cancer or lymphoma[45–56] (see supplementary tables 1-3).

Furthermore, biologic drug registers have enabled the study of outcomes in populations excluded from trials e.g. those with previous cancer[51,57] and the elderly.[42] They have also been able to comment on the risk of exposure to TNFi and other biologics during pregnancy.[58,59] The provision of further insights into the real-world safety of biologic therapies represents one of the most valuable aspects of register data.

Biologics Registers: Methodological Challenges

Developing and running a register requires thorough logistical and methodological planning to ensure completeness of data recording and adequate administrative support.

Patient recruitment and missing data

Recruitment into a register can be active or passive. Active recruitment presents more challenges since it involves an additional step and effort in the management of the patient, which when added to a busy clinic environment means that not all eligible patients may get recruited.

In order to ensure successful development, maintenance or consistent contribution to a register, it is important to have motivated physicians with a genuine interest and belief in the value of clinical data collection for research. Whereas often such contribution is completely voluntary, in some countries it is a mandatory duty to contribute a minimum amount of data (usually pre-specified on paper/electronic

forms) to biologics registers. The latter includes patient demographic and drug details, including adverse events and reasons for discontinuation. However, in busy clinical settings, accurately completing even the minimum amount of information requested, can pose a real challenge. This often leads to incomplete forms being submitted, which adds further to the administrative workload. In this respect, site reimbursement for recruiting patients into a register may provide an incentive for doing so. Passive recruitment is in theory simpler; however a potential challenge is the disconnection between the reporter and recorder as to why the data need to be captured. This, in turn, could risk incomplete or missing data that are likely to be a mixture of missing co-variate data or missing outcomes.

Actively encouraging registers to report the proportion of missing data especially when studying key outcomes is necessary and could motivate more complete data collection. Reducing the amount of missing data and improving the accuracy of the data collected is important for the quality of analyses and consequently the findings and conclusions made. For this, adequate administrative input, physician/collector encouragement and support, are crucial.

Type of data collection and input

Securing long-term and reliable funding to ensure register sustainability and having a robust, high-quality and ideally web-based platform for data input, access and extraction represent important challenges. The depth of data collected depends on the type of register and its design, dictated by the research question(s) under study. For example, some registers will include collection of data on patient and disease characteristics as well as treatment data and potential confounders. The actual process of data collection will depend on whether outcomes are reported or captured independent of the prescriber or both.

Many registers use data linkage as a useful way of enriching source data. Data linkage allows for further validation of events reported from source data and ensures more complete data, depending on the source of the linked data. It is particularly valuable when the linked data are in a mandatory national dataset, such as a

national death or cancer register. The ability to validate the events captured through a linked route will depend on the methods of the independent data source.

Biologics Registers: Analytical Challenges

Lack of randomization

The lack of randomization in patient allocation to treatment in routine clinical practice leads to confounding by indication, whereby observed outcomes may be related to the indication itself rather than any exposure, and this, along with the absence of a control group and channelling bias, necessitate appropriate and often advanced statistical techniques (e.g. propensity scoring) when analysing data. It should be acknowledged though that even with advanced statistical methods, these biases cannot be fully overcome. Confounding by indication often stems from clinical reasons driving treatment choice, as a result of physician and patient perceptions of disease severity, prognosis and treatment effect. However, other, 'extraneous' aspects including socio-economic factors also influence these decisions[60] and this requires appropriate epidemiological design, careful selection of control groups and analytical techniques.[60]

Time lag between first treatment exposure and eventual register analyses

The time lag (delay) from input of the drug into the market and the time needed to accumulate enough outcome data on which to base valid analyses needs to be considered. The analytical challenge relates both to the accumulated patient exposure and event latency relating to the drug. Finally, the issues of incomplete or missing data, missing patients (e.g. lost to follow-up) and the power to detect rare events need to be carefully considered, as even the largest national registers may still not be powered to be able to measure the risk of very rare events, such as certain individual cancer types. The latter, in particular, represents one of the major benefits of using combined register data.[46]

Pooled vs parallel analysis

A possible simple solution to the issue of low power within individual registers is data pooling or parallel analysis with meta-analysis. However, as a result of differences in the register designs, types of data collected, as well as differences in health care systems, geographical and population differences, careful consideration is necessary regarding the best way to approach this. Aside from inherent variations in patient characteristics (e.g. different genetic backgrounds), endemic diseases (e.g. tuberculosis, HIV), presence of co-morbid conditions and differences in access to biologics may affect disease severity at the onset of treatment and therefore the response to treatment. Therefore, simple data pooling to examine outcomes may not be an appropriate approach to study drug safety or effectiveness. Instead, parallel analysis of data may be more appropriate and insightful into differing factors. Furthermore, and beyond the type and nature of data collected, ethical restrictions and patient consent may be a further obstacle to data sharing and pooled analysis.

The recognition of these issues has resulted in the publication of points to consider by EULAR, when designing and establishing a biologics register (Box 1).[61] The differences in recruitment patterns, data collected (items and definitions) and biologic prescribing across registers is an important issue when pooling data together for analysis.[62] Subsequently, the EULAR Study Group for Registers and Observational Studies (RODS)[62] specifically set out to compare differences between patients starting biologics across Europe. This study, which involved 14 European bDMARD registers, highlighted that differences in disease severity do exist at the start of therapy, but also highlighted the issue of a lack of a common data model across Europe and the need to work further on harmonizing data collection across registers. In this sense, identifying a minimum core set of items to be collected is thus useful in providing a common platform for common data analysis across multiple registers. This forms the backbone for the EULAR Task Force on recommendations for the standardised content and structure of core data to facilitate patient care and observational research in RA.[63]

The ability to standardize data collection across registers can lead to better understanding of the reasons for heterogeneity in the results observed and discrepant conclusions from some registers[3] as well as improving the interpretation and comparison of class and drug-specific risks.[64] Existing initiatives involving pooled data analysis[25,27,28] have provided insights not just regarding the influence of intrinsic patient (e.g. age) and disease (e.g. antibody status) characteristics but also to extrinsic factors such as geographical and other influences and variations in treatment practice. The growing interest in pooling datasets together for common data analysis represents a potential future application of biologics registers that would increase their power and enable the provision of information on a more diverse patient population.[65,66]

Figure 2 summarises important strengths and challenges of biologic drug registers.

Making The Best Use Of Observational Drug Data

Many of the challenges/limitations discussed will inevitably be present but this is acceptable as long as there is transparency in methodology and limitations of analysis used.[67] It should be remembered that even discrepant findings can provide us with important information if study design, analysis and data reporting is given careful consideration.[3,68]

Future and novel applications

The emphasis of research questions and outcomes examined in biologics registers is changing over time, shifting from a focus on disease behaviour, improving disease activity and decreasing disability to treatment effectiveness in different disease groups[69] and on individualising treatment e.g. which biologic to choose after a patient experiences an inadequate response or an adverse event with a TNFi.[70] Although to date the majority of biologics registers started with recruitment of RA patients, over the years register data have extended to include biologic use for other conditions e.g. ankylosing spondylitis and psoriatic arthritis, enabling the study of important outcomes in these disease areas too.[71,72]

Platform for newly-emerging therapies

With up to 15 years of knowledge gained from biologic register data, this represents a platform for embarking on collection of data for biosimilars, new classes of biologics and other advanced therapies. Several national rheumatology societies have already produced position papers on the use of biosimilars recommending the registration of biosimilar-treated patients in registers for efficacy, safety and immunogenicity surveillance, following the strategy already ongoing for originators.[73–76]

Bridging the effectiveness–efficacy gap

Attempting to bridge the gap between effectiveness-efficacy i.e. reducing discrepancies identified between effectiveness (real life) and efficacy (ideal circumstances) and when evaluating new treatments would maximize the information gathered. Clinical trial data help us understand efficacy without the effect of confounding factors; however, efficacy across trial populations may not translate into equal effectiveness in individual, real-world patients. With comparative effectiveness research becoming increasingly important, clinical trials are unlikely to provide answers to many important questions, in contrast to observational biologics register data.[3] Furthermore, biologic registers could be of value in studying subsets of the population not adequately studied in clinical trials and to address effectiveness including cost-effectiveness of 3rd and 4th line biologics compared to earlier use in the treatment pathway.

Combined register-trial studies

With randomization being the only reliable method of controlling for confounding factors and enabling accurate comparisons of treatment groups, clinical trials represent a strong foundation for evidence-based medicine.[77] However, to run an adequately powered clinical trial requires high costs and this, along with other limitations, including the select population which may not represent average clinical practice patients are important problems. A possible solution would be to include a randomization module within a clinical register with unselected consecutive enrolment hence in a way making the best use of a prospective randomized trial

combined with a larger-scale clinical register.[77] Such an approach represents a potentially more efficient and cost-effective future application of a register making it possible to obtain more accurate answers to questions that clinical trial data alone would not have been able to provide.

Conclusions

Biologic drugs have had a ground-breaking effect on the treatment of RA; yet, the future of RA and its treatment does not solely rely on these. The intensified treatments and treat-to-target approaches that characterise current times on the background of emerging new therapies, necessitate high vigilance and carefully conducted studies to assess safety profiles, efficacy and effectiveness. The establishment of several national biologic registers globally to understand real-world effectiveness and safety beyond that observed in RCTs, fills an important gap in the literature, enhancing our understanding on real-life aspects of these therapies, their impact on disease progression and long-term outcomes. Their rich repository of data will have an ongoing role in complementing clinical trial data. Although challenges remain, with advanced methodologies and new technologies on the horizon, their potential for novel uses remains promising.

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Tables & figures to be included in the manuscript

Figure 1 (Timeline) European biologic registries in rheumatoid arthritis. The design and unique features of some of the larger European registries are summarized below (in alphabetic order): Antirheumatic Therapies in Sweden (ARTIS)[47,789,50]: Overseen by the Swedish Rheumatology Association and integrated into clinical practice. Allows linkage to external registries and multiple control groups. Includes data from two regional sub-registries (Southern Swedish Antirheumatic Therapy Group and Stockholm TNF Follow-up). The British Society for Rheumatology (BSR) Biologics Registry (BSRBR)[79]: Formed by an alliance between the BSR, the pharmaceutical industry and the University of Manchester. Initiated as a national prospective study that mandated registry enrolment for all biologic-treated patients. The BSRBR includes data from a parallel comparison group of patients with active rheumatoid arthritis (RA) treated with conventional DMARDs. It has external linkage with national mortality and malignancy registries. Danish National Biologic Registry (DANBIO)[80]: National quality of care registry designed to capture operational clinical data as part of routine care. Includes patients with RA, Psoriatic arthritis and ankylosing spondylitis followed longitudinally. Norwegian Disease-Modifying Antirheumatic Drug Registry (NOR-DMARD)[81]: Five-centre registry covering approximately one-third of the population in Norway. Includes all DMARD prescriptions to patients with inflammatory arthropathies, including RA. RA-Observation of Biologic Therapy (RABBIT)[51]: Nationwide prospective cohort study with an internal control group of DMARD switchers; after discontinuation of biologic treatment, the patients contribute to a second control group. Swiss Clinical Quality Management Programme for RA (SCQM-RA)[82]: Longitudinal population-based cohort of patients with RA, supported by the Swiss Society of Rheumatology. Recruitment is solely undertaken by rheumatologists. Patients included in SCQM-RA have more severe disease and receive more biologic agents than do RA patients in the general Swiss population. AIR, AutoImmunity and Rituximab; ATTRA, Registry of patients treated with anti-TNF drugs; BIOBADASER, Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología; BIOROSS, Russian national biologic registry; BioRx, Slovenian national biologic registry; DREAM, Dutch RA Monitoring registry; ERSBR, Estonian Society for Rheumatology Biologics Register; GISEA, Grupo Italiano di Studio Sulla Early Arthritis; HeRBT, Hellenic Registry for Biologic Therapies; HU-REGA, Hungarian Registry; HÜR-BIO, Hacettepe University Rheumatology Biologic Registry; ICEBIO, Iceland National Biologics Registry; LORHEN, Lombardy Rheumatology Network; MIRA, MabThera In RA; NARRAS, National Registry of Patients with RA; ORA, Orencia in RA; RABBIT, RA Observation of Biologic Therapy; RATIO, Research Axed on Tolerance of Biotherapies; REGATE, Longitudinal Study on Patients with RA and Study on Tolerance and Efficacy of Tocilizumab (also known as REGistry-RoAcTEmra); Reuma.pt, The Rheumatic Diseases Portuguese Register; ROB-FIN, National Register of Biologic Treatment in Finland; SCQM-RA, Swiss Clinical Quality Management Programme for RA.

Table 1. Examples of biologic registries in RA, their purpose, design and unique features.

REGISTRY	COUNTRY	PURPOSE	DESIGN & UNIQUE FEATURES
BSRBR[79]	United Kingdom	Established by the British Society for Rheumatology (BSR) to monitor patients with rheumatic diseases on biologics and evaluate long-term toxicity of these agents in clinical practice.	Nationwide registry, formed by an alliance between the BSR, the pharmaceutical industry and the University of Manchester. Designed as a national prospective study with patient enrolment being an essential part of the prescribing process. The registry includes recruitment and collection of data from a parallel comparison group of patients consisting of those with active RA treated with conventional DMARDs. It has external linkage with national mortality and malignancy registries.
ARTIS[47,78]	Sweden	Developed to provide data on patients on biologics following request by the Swedish Medical Product Agency to rheumatologists.	National registry. Overseen by the Swedish Rheumatology Association and integrated into clinical practice. Allows for multiple control groups to be used and linkage to external registries. Includes data from two regional registries (SSATG and STURE).

RABBIT[51]	Germany	Developed to assess the long-term safety of biologics agents.	Nationwide prospective cohort study with an internal control group of DMARD switchers; after discontinuation of treatment with biologics, the patients contribute to a second control group.
DANBIO[80]	Denmark	Developed to assess treatment effectiveness, adverse events and quality of life. Aimed to have clinical usefulness to rheumatologists during consultations, to improve quality of care.	National quality registry. Designed to capture operational clinical data as part of routine care. Includes patients with RA, PsA and AS followed longitudinally.
NOR-DMARD[81]	Norway	To assess the effectiveness and safety of DMARDs in inflammatory arthropathies.	Five-centre registry covering approximately a third of the population in Norway; includes all DMARD prescriptions to patients with inflammatory arthropathies including RA.
SCQM-RA[82]	Switzerland	Aims to improve quality of care for patients with RA through examination of outcomes in individual patients.	Longitudinal population-based cohort of RA patients; supported by the Swiss Society of Rheumatology. Recruitment is solely undertaken by rheumatologists. Patients included in SCQM-RA have more severe disease and receive more biologic agents compared to RA patients in the general population.

AS=Ankylosing Spondylitis; BSR=British Society of Rheumatology; PsA=Psoriatic arthritis;

Figure 2. Strengths and challenges of biologic registers.

Box 1. EULAR points to consider when establishing biologic registries. Adapted from Dixon et al., 2010[61]

Points to consider

1. ***General*** (e.g. defining scientific questions, considering sample sizes, follow-up needed)
2. ***Population to be targeted*** (e.g. defining eligibility criteria)
3. ***Data items to be collected, treatment and the treated condition*** (e.g. identifying a minimum core set of variables to be collected)
4. ***Data items to be collected, outcomes*** (e.g. ensuring outcomes are collected in a complete, robust and transparent manner)
5. ***Follow-up methods*** (e.g. ensuring similar methods to the exposed and comparison cohorts)
6. ***Data collection process and data collectors*** (e.g. defining who will be providing and entering data, defining and testing data capture and entry)
7. ***Data handling and storage, ethical and legal considerations*** (e.g. ensuring security of patient-identifiable information and compliance with local legislation)