Biologics registers in rheumatoid arthritis

Rebecca Davies

Kimme L Hyrich

Abstract

The introduction of biologic therapies has resulted in improved outcomes in patients with rheumatoid arthritis (RA), although there are concerns about the long-term safety of these drugs, specifically relating to lymphoma and serious infection. Biologics registers have been established worldwide to investigate the long-term safety and effectiveness of biologic drugs in inflammatory conditions such as RA.

To date, publications from biologics registers have focused mainly on anti-tumour necrosis factor (TNF) therapy, although reports of outcomes after other biologic classes, such as anti-interleukin-6 and anti-CD20 therapies, are increasing. The reports show that, in general, biologic therapies are effective in treatment of RA. However, registry data have shown that anti-TNF agents and rituximab are also associated with higher rates of serious infection. Lymphoma risk does not appear to increase in patients on anti-TNF therapy up to 5 years compared with patients given conventional synthetic disease-modifying anti-rheumatic drugs, but limited follow-up and numbers of patients taking other classes of biologic agents mean that lymphoma risk calculations are not yet available for those classes.

Moving forward, biologics registers will continue to capture long-term follow-up of biologic therapies in RA, as well as to incorporate new classes of biologics and other advanced therapies, such as the new kinase inhibitors. Furthermore, the introduction of biosimilars will require further evaluation of safety and effectiveness. This will extend our knowledge of the long-term safety and effectiveness of biologic drugs when used in 'real-life' situations and across conditions.

Keywords Anti-TNF therapy; biologics registers; drug safety; MRCP; rheumatoid arthritis; treatment outcome

Key points

- Biologics registers are longitudinal, observational and typically prospective cohort studies. They are able to recruit a large representative sample of patients being treated with biologics and follow them in the long term. However, they are often subject to loss to follow-up, missing data and confounding by indication. Considerations should include the cost of many years of data collection, the level of administrative support required and how to maintain detailed data collection
- Studies investigating the effectiveness of biologic therapies have been favourable across all classes of drug
- Infection risk is increased in patients taking anti-tumour necrosis factor therapies, particularly within the first 6 months of treatment
- Reports from biologics registers have not shown an increase in risk of non-Hodgkin's lymphoma after up to 5 years of follow-up

Introduction

Biologics (also known as biologic drugs or biologic agents) are therapeutic substances that were developed and are manufactured through biologic processes using human, animal or microorganism sources. This is in contrast to pharmaceutical drugs, which are manufactured using chemical processes.

In the treatment of inflammatory musculoskeletal diseases, effective biologics have been introduced that interfere with cytokine function, block co-stimulation of T cells and deplete B cells. The greatest experience is in the treatment of rheumatoid arthritis (RA). The introduction of biologics has resulted in improved outcomes in patients with RA, with good response being reported in approximately 60% of patients, and estimates of 20–42% achieving disease remission.

Although these agents are effective, there have been concerns about long-term safety, particularly with respect to lymphoma and serious infection. A number of randomized clinical trials (RCTs) have reported no increased risk of serious adverse events in RA patients treated with biologics compared with placebo. However, RCTs are inefficient in detecting rare or delayed-onset adverse events, and questions remain regarding long-term outcomes of biologic treatment.

In order to investigate the long-term safety and effectiveness of biologics in the context of inflammatory musculoskeletal conditions, a number of national biologics registers have been set up across Europe and in other nations.[1] Biologics registers are longitudinal, observational and typically prospective cohort studies.

Patients contribute data at regular time intervals either via self-report measures or from measures completed by physicians or nurses; these record adverse events and changes in therapy and markers of disease activity. Patients can also be followed through linkage with electronic health records. Registers often collect data about comparison cohorts of patients with the same disease who are being treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). However, some registers use general population data as their comparator. Registers should continue to follow patients after drug discontinuation or if they switch between biologics.

The strengths of biologics registers include their ability to recruit a large representative sample of patients being treated

Rebecca Davies *BA (Hons) MSc (Sport and Exercise Psychology) currently works as a Research Assistant at the University of Manchester, UK. Her research interests are in rheumatoid arthritis and juvenile idiopathic arthritis, specifically looking at safety of anti-TNF drugs. Competing interests: none declared.*

Kimme L Hyrich *MD PhD FRCPC is a Professor of Epidemiology at the University of Manchester and a Rheumatology Consultant at Central Manchester Foundation Trust, UK. Her research covers the effectiveness and safety of biologics in adult and paediatric inflammatory arthritis. Competing interests: none declared.*

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with these agents and to follow them in the long term. Weaknesses include loss to follow-up, missing data and confounding by indication (biologic agents tend to be prescribed for those with the most severe disease and so the worst prognosis). There are also methodological challenges in the running of biologics registers, including the cost of many years of data collection, the levels of administrative support required to sustain them, and the meticulous data collection and recording procedures, which are often difficult to sustain.[1]

Most research to date has focused on the first three licensed anti-tumour necrosis factor-α (anti-TNF) therapies for RA (etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira).[2] However, as the repertoire of biologics available for treatment of RA increases, including rituximab (RTX), an anti-CD20 monoclonal antibody, and tocilizumab (TCZ), an anti-interleukin-6 therapy, data have also started to emerge from biologic registers on these therapies. This chapter therefore briefly reviews key aspects of the safety and effectiveness of biologics reported from biologics registers.

Effectiveness in patients with RA

The effectiveness of anti-TNF therapies when used in routine care has been widely studied in biologics registers.[3] Generally, the results are favourable and largely in keeping with early results from RCTs. A recent review article has suggested that discontinuation rates of anti-TNF therapy at 6 months were similar across a number of registers; lack of response, rather than adverse outcomes, was the most common reason for early discontinuation. The UK British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA) reported a median drug survival of 3.3 years. Predictors of a good response include lower baseline disability, lower baseline disease activity and younger age.

The UK BSRBR-RA found that patients who switch to a second anti-TNF therapy after a poor response to a first one have higher rates of discontinuation on this second therapy, often for the same reason they discontinued the first treatment. Since the introduction of new classes of biologics, such as the B-cell-depleting agent RTX, there have been comparisons between switching to these newer drugs versus switching to a second anti-TNF agent. Studies from Spain, Switzerland and the UK have reported greater improvements in both clinical effectiveness and physical function over 12 months after switching to RTX rather than another anti-TNF drug.

More recent studies, such as the UK BSRBR-RA, have also reported good efficacy of RTX at 6 months, irrespective of whether patients were treated with RTX alone or in combination with methotrexate. Around 17% of patients achieved a European League Against Rheumatism (EULAR) 'good response', with 43% achieving 'moderate response'. Similarly, the Italian Gruppo Italiano di Studio sulla Early Arthritis (GISEA) study and the German Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) study reported an improvement in Disease Activity Score (DAS28) score at 12 and 36 months, respectively, in patients treated with RTX both with and without concomitant csDMARDs.

The efficacy of TCZ has also been shown in more recent publications. The Rheumatic Diseases Portuguese Register (www.rheuma.pt) found that patients treated with TCZ were more likely to achieve remission or low disease activity as measured by DAS28 scores, as well as a good EULAR response, when compared with an anti-TNF cohort. Boolean remission rates were comparable between the groups. The UK BSRBR-RA reported similar findings, with first-line TCZ users more likely to achieve DAS28 remission at 6 months than first line anti-TNF users; however, this was largely driven by greater improvements in C-reactive protein concentration (CRP) and erythrocyte sedimentation rate (ESR) as other improvements in other DAS components were comparable.

Safety in patients with rheumatoid arthritis

Infection

A review of safety in RA patients exposed to anti-TNF therapy found that infection rates with anti-TNF therapies were increased, particularly during the first few months of treatment, after which risk declined (Figure 1).[4] The risk of bacterial intracellular infections (e.g. *Listeria*, *Salmonella*) was also increased, but this can be improved via information advising patients to avoid high-risk foods. Skin infections including herpes zoster have been reported to increase in patients on anti-TNF therapy in the German RABBIT register as well as the UK BSRBR-RA. Data from registers have also confirmed an increased risk of tuberculosis in patients exposed to anti-TNF therapy, in particular monoclonal antibodies.

The main research into infection risk has been focused on anti-TNF therapies. However, in 2014 the Italian GISEA study reported that risk of serious infection increased in patients on RTX and concomitant methotrexate compared with patients on RTX alone.

Lymphoma

One of the most eagerly anticipated outcomes to emerge from biologics registers relates to risk of lymphoma. Over several decades, studies have reported an association between RA and an increased risk of non-Hodgkin's lymphoma (NHL). This appears to be related both to cumulative disease activity and previous exposure to immunosuppressive therapy. Hypothetically, anti-TNF therapy might further increase the risk of NHL (by immunosuppression) or reduce the risk (by reducing cumulative disease activity).

Analysis of the risk of NHL in the context of anti-TNF therapy is challenging because of confounding by indication (i.e. the drug is prescribed to those most at risk of developing NHL). Most analyses have employed a degree of adjustment for baseline differences between treated and untreated cohorts, and we are increasingly seeing the use of propensity models to account for a wide range of differences in patient characteristics at the start of treatment. Overall, reports from biologics registers to date have not shown an increase in risk of NHL, although mean follow-up periods have been short (often <5 years) (Table 1). More recently, the UK BSRBR-RA reported no increased risk of lymphoma for a median follow-up time of 8 years in patients on anti-TNF therapy compared with csDMARD therapy.[5]

The future

Biologics registers have extended our knowledge of the long-term safety and effectiveness of biologic therapy in patients with rheumatic disease. They will continue to accrue long-term follow-up data to address these issues, particularly with respect to long-term risk of cancer.

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