Biologics registers in rheumatoid arthritis

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Abstract

The introduction of biological 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 long-term safety as well as effectiveness of biologic drugs in inflammatory conditions such as RA.

To date, publications from biologics registers have focused mainly on anti-tumour necrosis factor therapy (anti-TNF agents). The reports show that anti-TNF agents are effective in the treatment of RA. However, they are also associated with higher rates of serious infection. Lymphoma risk does not appear to increase, although findings are limited by mean follow-up periods of less than 5 years.

Moving forward, biologics registers will continue to capture long-term follow-up of anti-TNF drugs in RA, as well as incorporating new classes of biologics and other musculoskeletal diseases. This will further 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; rheumatoid arthritis; treatment outcome

Introduction

Biologics (also known as biological drugs or biologic agents) are therapeutic substances that were developed and are manufactured through biological 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 (MSK) diseases, effective biologic agents 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.[1–3] Although these agents are efficacious, there have been concerns about long-term safety, particularly with respect to lymphoma and serious infection.[4] A number of randomized clinical trials (RCTs) reported no increased risk of serious adverse events (SAEs) in biologic-treated RA patients when compared with placebo.[3,5,6] 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 long-term safety and effectiveness of biologic agents in the context of inflammatory MSK conditions, a number of national biologics registers have been set up across Europe and other nations.[7] 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, which record adverse events, changes to therapy, and markers of disease activity. Patients can also be followed through linkage with electronic health records. Often registers collect data about comparison cohorts of patients with the same disease being treated with non-biologic disease-modifying drugs (nbDMARDs). However, some registers use general population data as their comparator. Registers should continue to follow patients after drug discontinuation or if they switch between biologic agents. The strengths of biologics registers include their ability to recruit a large representative sample of patients being treated with these agents and to follow them 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).

The majority of research to date has focused on the first three licensed anti-tumour necrosis factor-alpha (anti-TNF) therapies for RA (etanercept [ETN], infliximab [INF] and adalimumab [ADA]).[4] This chapter will therefore review briefly key aspects of the safety and effectiveness of these therapies reported across a number of 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. 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 was the most common reason for early discontinuation rather than adverse outcomes.[8] The UK British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA) reported a median drug survival of 3.3 years.[9] Predictors of a good response include lower baseline disability, lower baseline disease activity and younger age.[10–12]

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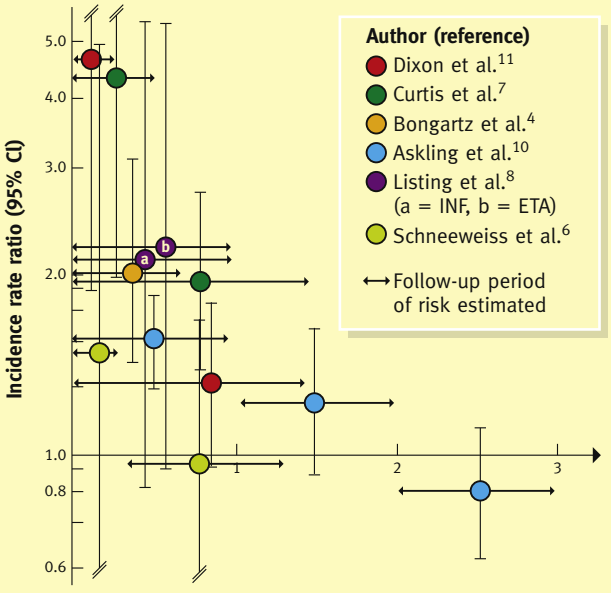
Relative risk of serious infection in patients with rheumatoid arthritis treated with tumour necrosis factor antagonists, by time since start of treatment[17]



95% CI, 95% confidence interval; INF, infliximab; ETN, etanercept

Figure 1 From Askling J, Dixon W. The safety of anti-tumour necrosis factor therapy in rheumatoid arthritis. *Current Opinion in Rheumatology* 2008; **20(2)**. Reproduced with kind permission from Wolters Kluwer Health.

The UK BSRBR-RA found that patients who switch to a second anti-TNF therapy following a poor response to a first have higher rates of discontinuation on this second therapy, often for the same reason they discontinued the first treatment.[13] Since the introduction of new classes of biologic drugs, such as the B-cell depleting agent, rituximab (RTX), there have been comparisons between switching to these newer drugs versus switching to a second anti-TNF. Studies from Spain, Switzerland and the UK have reported greater improvements in both clinical effectiveness and physical function over 12 months in patients switching to RTX rather than another anti-TNF drug.[14–16]

Safety in patients with RA

Infection

A review of safety in RA patients exposed to anti-TNF therapy found that infection rates with anti-TNF therapies are increased, particularly during the first few months of treatment, after which the risk declines[17–21] (Figure 1). The risk of bacterial intracellular infections, (e.g. *Listeria* and *Salmonella*) is also increased, but can be improved through information advising patients to avoid high-risk foods.[22] Skin infections including herpes zoster have also been reported to be increased in patients on anti-TNF therapy in the German Rheumatoid Arthritis-Observation of Biologic Therapy (RABBIT) as well as the UK BSRBR-RA.[23,24] Data from registers has also confirmed the increased risk of tuberculosis in patients exposed to anti-TNF therapy, in particular monoclonal antibodies.[25,26]

Lymphoma

One of the most eagerly anticipated outcomes to emerge from biologics registers is that of the risk of lymphoma. Over several decades, studies have reported an association between RA and an increased risk of non-Hodgkin's lymphoma (NHL).[27,28] This appears to be related both to cumulative disease activity[29] and previous exposure to immunosuppressive therapy.[30] 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 due to confounding by indication (i.e. the drug is prescribed to those most at risk of developing an NHL). Most analyses have employed a degree of adjustment for baseline differences between treated and untreated cohorts, and increasingly we are seeing the use of propensity models to account for a wide range of differences in patient characteristics at the start of treatment.[31] Overall, reports from biologics registers to date have

Summary of lymphoma risk across four studies

Author	Data source	Study design	Comparator group	Results
Wolfe et al.[32]	NDB	National prospective cohort study of RA patients on anti-TNF therapy	Anti-TNF naïve RA patients	**Odds ratio (OR)** Anti-TNF vs. comparator: 1.0 (95% CI 0.6, 1.8)
Askling et al.[33]	ARTIS	National cohort of Swedish patients with RA, anti-TNF treated and naive	Anti-TNF naïve RA patients	**Relative risk (RR)** Anti-TNF vs. comparator: 1.35 (95% CI 0.82, 2.11)
Mercer et al.[34]	BSRBR-RA	National prospective cohort study of RA patients on anti-TNF therapy	Anti-TNF naïve RA patients	**Hazard ratio (HR)** Anti-TNF vs. comparator: 1.13 (95% CI 0.55, 2.31)
Dreyer et al.[35]	DANBIO	National prospective register collecting data on rheumatology patients receiving routine care	Anti-TNF naïve RA patients	**Hazard ratio (HR)** Anti-TNF vs. comparator: 0.92 (95% CI 0.29, 2.92)

Abbreviations: Anti-TNF, anti-tumour necrosis factor therapy; ARTIS, Anti-Rheumatic Therapy in Sweden; BSRBR-RA, British Society for Rheumatology Biologics Register-Rheumatoid Arthritis; DANBIO, Danish Registry for Biologic Therapies in Rheumatology; NDB, National Data Bank for Rheumatic Diseases; RA, rheumatoid arthritis; 95% CI, 95% confidence interval.

Table 1