**The BSRBR-RA at 15 years**

**Strap line: Providing Real-World Insight into the Effectiveness and Safety of Biologic Therapies**

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The advent of anti-TNF therapies for rheumatoid arthritis (RA) has produced a very significant advance in the way rheumatologists treat their patients, offering the chance of long-term remission for many more people than was previously thought possible. For those clinicians below the age of 40 years, it is perhaps impossible to conceive a world where these therapies were not available.

The British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) was launched when anti-TNF therapies became available; a crucial aspect of the original BSR guidelines to all UK rheumatologists on the use of anti-TNF in RA was enrolment on a national register as an essential part of the prescribing process. The register was established in 2001 when an alliance was formed between the BSR, the pharmaceutical industry and the University of Manchester, where the register is held. As we celebrate the 15 year anniversary of the BSRBR-RA, it is perhaps time to reflect on the information that has emerged from the register. Here we celebrate some of the register’s key findings by reviewing 8 papers published in this Journal which have focussed on the safety and effectiveness of anti-TNF therapies in patients with RA. These papers sit within a sizeable collection published from the BSRBR-RA both within this Journal and the worldwide literature that is available from the BSRBR-RA website [1].

Many papers from the BSRBR-RA have focussed on the effectiveness of biologic therapies when used in routine clinical practice, away from the confines of a clinical trial. It is clinically important to identify groups of patients who might preferentially benefit from anti-TNF therapy. In a 2006 paper, Hyrich et al. studied 2879 patients with RA (mean age 55 years, mean disease duration 14 years) starting their first treatment with etanercept or infliximab [2]. After 6 months, 50% had a moderate response and 18% had a good EULAR response, and 9% were in remission. There was no overall difference in response rate between the two anti-TNF therapies. Both current smokers and more disabled patients (high baseline HAQ score) had poorer response rates and women were less likely to achieve remission. Patients concurrently receiving anti-inflammatories or methotrexate were more likely to respond to anti-TNF. Age, disease duration, rheumatoid factor and the previous number of DMARDs did not predict response to either drug.

The effect of switching between anti-TNF therapies was the subject of a 2008 paper that identified 868 RA patients with inefficacy to a first anti-TNF based on clinician opinion and/or DAS score [3]. Fifty five percent stopped their first anti-TNF treatment, with 69% of these switching to a second anti-TNF agent. The authors demonstrated that both patients who continued and those who switched anti-TNF therapy had improvements in HAQ over the 12 months, with a trend towards more improvement among those who switched, in contrast to patients who discontinued all biologic therapy.

The benefit of anti-TNF therapy in RA patients with moderate disease activity was assessed in an analysis of 4687 anti-TNF / 344 DMARD patients with high disease and 224 anti-TNF- / 300 DMARD-treated patients with moderate disease activity despite treatment with two standard DMARDs [4]. The mean adjusted change in HAQ over 12 months was similar in patients starting anti-TNF with moderate and high disease activity at baseline. This lack of dependence of initial disease severity on response suggests that substantial benefits may be gained by treating moderately active disease despite standard DMARD therapy.

A 2011 paper considered how the disease characteristics of patients starting anti-TNF therapy have changed over time [5]. Among a total of 11216 BSRBR-RA patients starting their first anti-TNF between 2001 and 2008, mean disease activity and disability scores decreased year-on-year. Patients were also receiving the treatments earlier, with the proportion of patients starting within the first 5 years following diagnosis increasing, although the mean disease duration in 2008 remained high at 11 years. Year-on-year, the proportion of patients achieving EULAR good responses and remission also increased.

Balanced with obtaining a better understanding of the effectiveness of these therapies in real-world practice is gaining a better understanding of their safety profile. A particular concern when anti-TNF therapy was first introduced was serious infection, and in a 2011 paper, Galloway and colleagues demonstrated an increased risk of serious infection in patients with RA especially in the first 6 months of treatment [6]. Using data from the BSRBR-RA they compared the risk of serious infection between 11 798 anti-TNF-treated patients and 3598 non-biologic DMARD treated patients. The adjusted hazard ratio of serious infection in the anti-TNF cohort was 1.2 (95% CI 1.1, 1.5). Reassuringly mortality within 30 days of serious infection was 50% lower in the anti-TNF cohort. The authors suggested that the small but significant overall risk of serious infection with anti-TNF therapy should be balanced against the risks associated with poor disease control or alternative treatments.

The BSRBR-RA has also published the results of analyses focusing on the risk of other adverse events, including exposure to anti-TNF in pregnancy, the risk of pulmonary embolism, and the risk of psoriasis [1]. However, perhaps of particular concern has been whether anti-TNF therapy is associated with an increased cancer risk. To date, analyses of data from the BSRBR-RA have not identified an increased risk of non-melanoma skin cancer [7] or solid organ cancer [8]. A small study limited to patients with a history of malignancy prior to starting anti-TNF has also not found an increased risk of new therapies among this selected group of patients compared to those remaining on standard DMARD therapy [9].

The BSRBR-RA has yielded considerable clinical guidance over the years. However, the findings reported above have been possible only because of the clinicians and patients who have taken the time and trouble to participate in the registry. We hope you will agree that your efforts have been worthwhile, and that you will continue to contribute over the years to come, as clinical questions regarding safety and effectiveness of both long term anti-TNF use and newer biologic therapies will continue to develop.

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**Conflict of interest**

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