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Concise report

# The EULAR Study Group for Registers and Observational Drug Studies: comparability of the patient case mix in the European biologic disease modifying anti-rheumatic drug registers

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## Abstract

**Objective.** Under the auspices of the European League Against Rheumatism (EULAR), a study group of investigators representing European biologic DMARD (bDMARD) registers was convened. The purpose of this initial assessment was to collect and compare a cross section of patient characteristics and collate information on the availability of potential confounders within these registers.

**Methods.** Baseline characteristics of patients starting their first bDMARD in an arbitrary year (2008) for the treatment of RA, including demographic and disease characteristics, bDMARD drug details and co-morbidities, were collected and compared across 14 European bDMARD registers.

**Results.** A total of 5320 patients were included. Half the registers had restricted recruitment to certain bDMARDs during the study year. All registers' collected data on age, gender, disease duration, seropositivity for IgM-RF and 28-joint DAS (DAS28). The mean DAS28 ranged from 4.2 to 6.6 and the mean HAQ from 0.8 to 1.9. Current smoking ranged from 9% to 34%. Nine registers reported co-morbidities with varying prevalence.

**Conclusion.** In addition to demonstrating European-wide collaboration across rheumatology bDMARD registers, this assessment identified differences in prescribing patterns, recruitment strategies and data

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items collected. These differences need to be considered when applying strategies for combined analysis. The lack of a common data model across Europe calls for further work to harmonize data collection across registers.

**Key words:** rheumatoid arthritis, epidemiology, biologic therapies, outcome measures, study design.

**Rheumatology key messages**

- European RA biologic registers vary in design, recruitment and data items collected.
- Patient characteristics at the start of biologic therapies vary across European RA biologic registers.
- Patient and register differences are important when combining RA registers to study rare outcomes.

## Introduction

While biologic DMARDs (bDMARDs) have significantly improved outcomes for patients with RA, rare adverse events remain a concern. Many European countries have set up national bDMARD registers to evaluate long-term outcomes. However, despite large patient numbers in these registers, it is likely that individually they lack power to confidently rule out moderate yet clinically meaningful increases in risks of rare potential adverse events, such as lymphoma [1–6]. Under the auspices of the European League Against Rheumatism (EULAR), a study group of investigators representing European bDMARD registers was convened to explore the feasibility of combined analyses.

A challenge when combining large datasets is understanding the extent of heterogeneity, particularly as marked differences in important confounders may mask potential exposure effects on outcome. Across Europe there are significant differences in the use of bDMARDs for RA related to acceptability, availability and affordability [7, 8]. These may result in variations in patient disease activity, duration or severity at the start of bDMARD therapy, which could lead to differences in the expected rates of adverse events. This is particularly important since certain adverse events, such as lymphoma, have been linked to disease activity; others, such as serious infection risk, are also linked to a number of co-morbidities [9–12]. Modern statistical techniques can allow for such variation and control for these potential confounders, but more differences may exist across countries regarding other unmeasured confounders. Therefore, information on these variables for statistical adjustment is important.

With these challenges in mind, the purpose of this initial assessment was to (i) identify and create a collaborative group of European bDMARD registers, (ii) collect and compare information on characteristics of patients across these registers and (iii) collate information on the availability of important potential confounders within these registers.

## Methods

Eighteen European national registers were invited to participate in this analysis to provide cross-sectional information on all registered patients starting their first bDMARD between 1 January 2008 and 31 December 2008 for the treatment of RA. Summative baseline data were collected from each register, including patient demographics (age, gender, smoking status), disease characteristics (disease duration, seropositivity for IgM-RF, disease activity measures), current anti-rheumatic treatment [patients starting each bDMARD, patients on concomitant MTX and mean dosage, patients on oral prednisolone and mean dosage, patients on other non-biologic DMARDs (nbDMARDs) and number of previous nbDMARDs] and important co-morbidities (hypertension, cardiovascular disease, diabetes, chronic obstructive lung disease, depression, previous cancer, previous tuberculosis).

Each register entered values into a template Excel (2007; Microsoft, Redmond, WA, USA) spreadsheet, including the amount of missing data for each variable. The data were then emailed to the analysis coordinator in the UK and collated for comparison. All registers were approved and all patients consented according to the local ethical approval for each register. No additional ethics approval was required to undertake the current study.

## Results

### Characteristics of the participating registers

Fourteen European bDMARD registers agreed to take part in this initial exercise. All registers recruited adult patients with a diagnosis of RA starting a biologic and no registers had any exclusion criteria, with the exception of some registers limiting recruitment to certain biologic drugs only (supplementary Table S1, available at *Rheumatology* Online). A total of 5320 patients with RA initiating their first ever bDMARD were included (Table 1).

All registers collected data on age, gender, disease duration, seropositivity for IgM-RF and 28-joint DAS (DAS28) (Table 2). The majority also collected data on the individual components of the DAS28: swollen joint count, tender joint count, CRP, ESR and patient global assessment. Baseline MTX use was captured in all 14 registers. Oral prednisolone use was captured in 13 registers. Doses of MTX and prednisolone were captured in seven and eight registers, respectively. All registers but one collected co-morbidity data. Four registers collected co-morbidity data but were unable to provide the details for this analysis; reasons for this included a large proportion of missing data in one register. In the other three registers, these

TABLE 1 RA patients starting a first biologic DMARD in 14 European biologic DMARD registers in 2008

| Country | Register | *n* | Adalimumab, *n* (%) | Etanercept, *n* (%) | Infliximab, *n* (%) | Rituximab, *n* (%) | Abatacept, *n* (%) | Tocilizumab, *n* (%) | Anakinra, *n* (%) | Certolizumab pegol, *n* (%) | Golimumab, *n* (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Czech Republic | ATTRA | 267 | 95 (36) | 91 (34) | 54 (20) | 12 (4) | 15 (6) | 0 | 0 | 0 | 0 |
| Denmark | DANBIO | 624 | 193 (31) | 177 (28) | 235 (38) | 16 (3) | 2 (<1) | 0 | 1 (<1) | 0 | 0 |
| Finland | ROB-FIN | 206 | 86 (42) | 66 (32) | 25 (12) | 29 (14) | 0 | 0 | 0 | 0 | 0 |
| Germany[a] | RABBIT | 533 | 220 (41) | 168 (32) | 48 (9) | 26 (5) | 4 (<1) | 54 (10) | 0 | 6 (1) | 7 (1) |
| Hungary | HU-REGAR | 41 | 17 (41) | 16 (39) | 8 (20) | 0 | 0 | 0 | 0 | 0 | 0 |
| Italy | GISEA | 425 | 123 (29) | 236 (56) | 35 (8) | 19 (4) | 8 (2) | 0 | 4 (1) | 0 | 0 |
| Netherlands | DREAM | 266 | 104 (39) | 142 (53) | 16 (6) | 4 (2) | 0 | 0 | 0 | 0 | 0 |
| Norway | NOR-DMARD | 142 | 13 (9) | 93 (65) | 29 (20) | 7 (5) | 0 | 0 | 0 | 0 | 0 |
| Portugal | Reuma.pt | 107 | 20 (19) | 56 (52) | 25 (23) | 5 (5) | 0 | 1 (1) | 0 | 0 | 0 |
| Slovenia | BioRx.si | 141 | 66 (47) | 56 (40) | 17 (12) | 0 | 0 | 0 | 2 (1) | 0 | 0 |
| Spain | BIOBADASER | 210 | 55 (26) | 84 (40) | 59 (28) | 11 (5) | 1 (<1) | 0 | 0 | 0 | 0 |
| Sweden | ARTIS | 1152 | 238 (20) | 547 (47) | 263 (23) | 93 (8) | 8 (1) | 2 (<1) | 1 (<1) | 0 | 0 |
| Switzerland | SCQM-RA | 809 | 385 (48) | 246 (30) | 137 (17) | 16 (2) | 23 (3) | 1 (<1) | 0 | 1 (<1) | 0 |
| United Kingdom | BSRBR-RA | 397 | 385 (97) | 0 | 0 | 12 (3) | 0 | 0 | 0 | 0 | 0 |
| TOTAL | | 5320 | 2000 | 1978 | 951 | 250 | 61 | 58 | 8 | 7 | 7 |

[a]Data from Germany represent patients recruited in 2009 due to recruitment cessation in 2008. *n*: number of patients in the register.

data are not contained within the registers but are available through national record linkage, which could not be performed for the purpose of this analysis.

### Characteristics of bDMARD initiators

Mean age at the start of the first bDMARD was in the mid-50s in all studies, with proportionally more female participants (Table 2). Average disease duration ranged from 8 years in the Netherlands, Spain and Switzerland to 13 years in Finland. The percentage of IgM-RF-seropositive patients ranged from 59% in the UK to 92% in Hungary. Current smokers ranged from 9% in Portugal to 34% in Switzerland. The proportion of patients ever to have smoked ranged from 23% in Portugal to 60% in the UK and 61% in Italy. Disease activity varied across the registers: mean DAS28 ranged from 4.2 in Switzerland to 6.6 in Slovenia and mean HAQ ranged from 0.8 in Norway (modified HAQ) and 0.9 in Switzerland to 1.9 in the UK.

Concomitant MTX use at baseline ranged from 41% in Switzerland to 91% in Slovenia. The use of other non-MTX nbDMARDs ranged from 8% in Norway to 65% in Finland. The mean number of previous DMARDs (reported in nine registers) ranged from two in Italy and Norway to four in Slovenia. There was also variability in the frequency of co-morbidities (Table 2). The proportion of patients with hypertension ranged from 8% of patients in Switzerland to 39% of patients in Germany. Depression ranged from 1% in Norway to 18% in Sweden and 20% in the UK.

## Discussion

This first collaboration of the EULAR Study Group for Registers and Observational Drug Studies has been a success with respect to participation; 14 registers provided detailed summative statistics on patients commencing their first bDMARD during a single calendar year. A single calendar year was chosen in order to limit patient variability in relation to calendar year, as it is known that patients who have started bDMARD therapies over the years have also changed even within a single country [13, 14]. The chosen date was arbitrary but did reflect the midway point between the start of many registers and the date of the current analysis. It is likely that the mean value of many of the data elements would have differed if an alternative year had been chosen, but the main finding of differences between registers and patients would likely still have emerged.

The different bDMARDs recruited to each register may represent the differential use of these agents in some countries, but it also highlights the different study designs of the registers. For example, the UK register was designed as a prospective cohort study with planned sample size recruitment; only certain cohorts were open in 2008. This is compared with Denmark, Sweden and Switzerland, where recruitment is built into the routine care of patients, or Spain, where all patients at participating centres prescribed bDMARDs are included. Ultimately this may introduce an element of selection bias into certain registers and therefore we cannot comment on the full

**Table 2** Baseline characteristics and co-morbidities of patients starting a first biologic DMARD in 2008

| | Czech Republic [ATTRA] ($n = 267$) | Denmark [DANBIO] ($n = 624$) | Finland [ROB-FIN] ($n = 206$) | Germany[a] [RABBIT] ($n = 533$) | Hungary [HU-REGAR] ($n = 41$) | Italy [GISEA] ($n = 425$) | Netherlands [DREAM] ($n = 266$) | Norway [NOR-DMARD] ($n = 142$) | Portugal [Reuma.pt] ($n = 107$) | Slovenia [BioRx.si] ($n = 141$) | Spain [BIOBADASER] ($n = 210$) | Sweden [ARTIS] ($n = 1152$) | Switzerland [SCQM-RA] ($n = 809$) | UK [BSRBR-RA] ($n = 397$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age, mean (S.D.), years | 52 (12) | 56 (13) | 55 (13) | 56 (12) | 51 (13) | 54 (14) | 55 (12) | 52 (13) | 55 (14) | 53 (11) | 55 (13) | 57 (14) | 54 (15) | 57 (13) |
| Male, % | 14 | 24 | 27 | 24 | 27 | 23 | 30 | 25 | 9 | 20 | 21 | 23 | 25 | 20 |
| Disease duration, mean (S.D.), years | 10 (9) | 9 (9) | 13 (10) | 10 (9) | 9 (8) | 9 (8) | 8 (8) | 9 (10) | 12 (10) | 9 (7) | 8(8) | 11 (11) | 8 (9) | 12 (9) |
| Seropositive for IgM-RF, % | 66 | 75 | 85 | 75 | 92 | 67 | 71 | 75 | 77 | 82 | 85 | 77 | 71 | 59 |
| HAQ (0–3), mean (S.D.) | 1.5 (0.6) | 1.2 (0.7) | 1.0 (0.9) | 1.3 (0.6) | 1.5 (0.5) | 1.1 (0.8) | 1.2 (0.6) | 0.8[b] (0.5) | 1.5 (0.7) | — | — | 1.2 (0.7) | 0.9 (0.7) | 1.9 (0.6) |
| DAS28 (CRP or ESR based, four variables), mean (S.D.) | 6.3 (0.9) | 4.9 (1.2) | 4.5 (1.1) | 5.2 (1.3) | 6.2 (0.9) | 4.8 (2.2) | 4.9 (1.3) | 4.6 (1.3) | 5.7 (1.4) | 6.6 (0.9) | 5.2 (1.3) | 5.1 (1.3) | 4.2 (2.1) | 6.3 (1.0) |
| Pain VAS (0–100), mean (S.D.) | — | 56 (23) | 52 (25) | 58 (23) | — | 54 (28) | 58 (23) | 53 (24) | 51 (30) | — | — | 56 (23) | 43 (29) | — |
| Doctor's global (0–100), mean (S.D.) | — | 40 (21) | 42 (22) | — | 58 (14) | 40 (28) | 55 (18) | 39 (17) | 52 (25) | 58 (29) | — | — | 55 (NA) | — |
| MTX concomitant (yes), % | 71 | 63 | 57 | 52 | 79 | 53 | 77 | 71 | 77 | 91 | 65 | 73 | 41 | 62 |
| Oral prednisolone (yes), % | 32 | 20 | 72 | 83 | — | 26 | 38 | 54 | 72 | 52 | 66 | 56 | 51 | 30 |
| Previous DMARDs, *n* (%) | 3.5 (1.7) | 3.4 (1.8) | — | 2.6 (1.0) | — | 2.0 (1.2) | 2.7 (1.1) | 2.0 (1.4) | 1.7 (1.3) | 4.0 (1.3) | — | — | 1 (1–2)[c] | 3.3 (1.2) |
| Current smoker, % | — | 24 | — | 22 | — | 24 | — | 25 | 9 | 16 | 15 | — | 34 | 21 |
| Ever smoker, % | — | 30 | — | 54 | — | 61 | — | 59 | 23 | 26 | — | — | — | 60 |
| Hypertension, % | NP | NP | NP | 39 | NM | 22 | NP | 11 | 37 | 33 | 25 | 14 | 8 | 37 |
| Cardiovascular disease, % | NP | NP | NP | 5 | NM | 5 | NP | 5 | 10 | 4 | 4 | 11 | 4 | 4 |
| Diabetes, % | NP | NP | NP | 9 | NM | 6 | NP | 7 | 9 | 6 | 7 | 5 | 1 | 7 |
| Chronic obstructive lung disease, % | NP | NP | NP | 4 | NM | 4 | NP | 2 | 5 | 1 | 3 | 3 | 2 | 4 |
| Depression, % | NP | NP | NP | 6 | NM | 3 | NP | 1 | 5 | 10 | 4 | 18 | 2 | 20 |
| Previous cancer (%) | NP | NP | NP | 5 | NM | 1 | NP | 2 | 1 | 3 | 3 | 12 | 0 | 3 |
| Previous TB, % | NP | NP | NP | 4 | NM | 10 | NP | 0 | 3 | 0 | 5 | 1 | 0 | 4 |

[a]Data from Germany represent patients recruited in 2009 due to recruitment cessation in 2008. [b]The MHAQ was used instead of the HAQ for Norway [NOR-DMARD]. [c]Median (IQR) presented. Percentages exclude missing data. DAS28: 28-joint DAS; MHAQ: modified HAQ; NA: not available; NM: no measure of co-morbidity; NP: co-morbidities measured but not presented; TB: tuberculosis; VAS: visual analogue scale.

degree of overlap (or not) between registers. Furthermore, total recruitment figures and proportions by drug cannot be interpreted as representative of the comparative use of such drugs across Europe.

Despite differences in registration criteria, all patients included were starting their first bDMARD following failure of nbDMARDs and thus should be at a comparable point in disease progression. Therefore most differences should not be explained solely by the choice of drugs under recruitment. Instead, prescribing guidelines, local practice and cultural differences may influence differences across Europe [7, 8]. In this study, DAS28 values were lowest in Finland, Norway and Switzerland and highest in the Czech Republic, Slovenia and the UK. It has been previously noted that the UK has strict guidelines on bDMARDs, limited to those with persistently high disease activity (DAS28 $>5.1$) despite two nbDMARDs. In contrast, Denmark and Norway are recognized as having more liberal guidelines. An early analysis found that up to 50% of patients starting a bDMARD in the years 2001–3 would not have been eligible for this treatment had they been resident in the UK [15–17]. Compared with the UK, Slovenia has a lower DAS28 threshold of 4.2 for commencing the first bDMARD. However, it also specifies at least eight joints to be affected, which may explain the high DAS28 in these patients [18].

One of the most important predictors of future adverse events may be patient co-morbidities at the start of treatment. There were differences in co-morbidities recorded across studies, including which co-morbidities were recorded and how. For example, Sweden defined depression using linked patient records of hospitalizations, primary care outpatient visits and prescriptions and therefore may also include patients prescribed tricyclic antidepressants for chronic pain. In comparison, the UK physician is asked to record whether a patient has ever had depression. These discrepancies highlight that while there may be true differences in the rates of certain co-morbidities across populations, it is also possible that a degree of artificial difference may be introduced through individual register methodology and design. This exercise also highlighted that study design has resulted in data on other key potential confounders, such as smoking status, being unavailable in some registers.

While this initial exercise was successful in assessing the comparability of patient populations, data items collected and data definitions, it will be challenging moving forward to find the most effective way to combine these data given the observed differences, considering that a simple pooling of data will prove problematic. However, given the need to understand the risk of rare outcomes, a combined approach is imperative and several different approaches will be considered, including combining only similar registers for less rare outcomes, different statistical methods to account for differences in patient populations and nested case–control design. Work in this area is progressing and two collaborative analyses (one in melanoma and one in lymphoma) are under way.

The purpose of this initial exercise was to understand the availability of key data on bDMARD exposure and differences in patient populations across Europe and how they might influence combined analyses of rare adverse events. It has identified variations in prescribing patterns, recruitment strategies and data items collected. Differences in patient populations have also been identified in terms of disease activity and co-morbidities, which may lead to disparity in expected adverse event rates. While this initial analysis is an overview of the baseline characteristics and not a long-term assessment of safety, it is important that all registers consider collecting information on the confounding baseline characteristics so they can be accounted for in the future. Work is ongoing within the EULAR that aims to harmonize both data domains as well as data collection within domains across future RA cohort studies [19, 20]. A challenge now for investigators is to identify the most effective way to combine these data given the observed differences and, on the basis of these differences, to work towards harmonization in methods of data collection across European rheumatology.

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## Supplementary data

Supplementary data are available at *Rheumatology* Online.

## References

1 Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis 2009;68:1136–45.

2 Mercer LK, Lunt M, Low AS *et al*. The risk of lymphoma in patients receiving anti-tumor necrosis factor therapy for rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register – Rheumatoid Arthritis. Arthritis Rheum 2012;64(10 Suppl):S680.

3 Setoguchi S, Solomon DH, Weinblatt ME *et al*. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum 2006;54:2757–64.

4 Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum 2007;56:1433–9.

5 Askling J, Baecklund E, Granath F *et al*. Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. Ann Rheum Dis 2009;68:648–53.

6 Dreyer L, Mellemkjaer L, Andersen AR *et al*. Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritides – a follow-up study from the DANBIO Registry. Ann Rheum Dis 2013;72:79–82.

7 Putrik P, Ramiro S, Kvien TK *et al*. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Ann Rheum Dis 2014;73:198–206.

8 Putrik P, Ramiro S, Kvien TK *et al*. Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth? Ann Rheum Dis 2014;73:2010–11.

9 Galloway JB, Hyrich KL, Mercer LK *et al*. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology 2011;50:124–31.

10 Zink A, Manger B, Kaufmann J *et al*. Evaluation of the RABBIT Risk Score for serious infections. Ann Rheum Dis 2014;73:1673–6.

11 Atzeni F, Sarzi-Puttini P, Botsios C *et al*. Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: comparison of adalimumab, etanercept and infliximab in the GISEA registry. Autoimmunity Rev 2012;12:225–9.

12 Baecklund E, Iliadou A, Askling J *et al*. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum 2006;54:692–701.

13 Hetland ML, Lindegaard HM, Hansen A *et al*. Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. Ann Rheum Dis 2008;67:1023–6.

14 Hyrich KL, Watson KD, Lunt M, Symmons DP. British Society for Rheumatology Biologics Register. Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008. Rheumatology 2011;50:117–23.

15 Hjardem E, Hetland ML, Ostergaard M *et al*. Prescription practice of biological drugs in rheumatoid arthritis during the first 3 years of post-marketing use in Denmark and Norway: criteria are becoming less stringent. Ann Rheum Dis 2005;64:1220–3.

16 Deighton C, Hyrich K. International guidelines on access to biologic therapy: why the differences and which is best? Nat Clin Pract Rheumatol 2008;4:520–1.

17 Deighton C, Hyrich K. Why do the French get much greater access to anti-TNF than the British? Vive la différence? Pas nécessairement. Rheumatology 2008;47:1600–2.

18 Orlewska E, Ancuta I, Anic B *et al*. Access to biologic treatment for rheumatoid arthritis in Central and Eastern European (CEE) countries. Med Sci Monit 2011;17:SR1–13.

19 Dixon WG, Carmona L, Finckh A *et al*. EULAR points to consider when establishing, analysing and reporting safety data of biologics registers in rheumatology. Ann Rheum Dis 2010;69:1596–602.

20 Radner H, Hyrich K, Dixon WG, Askling J. On behalf of EULAR Study Group for Registers and Observational Drug Studies. Consistency and usefulness of data items across European rheumatoid arthritis clinical cohorts and registers. Ann Rheum Dis 2014;73(Suppl 2):338.