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## CONCISE REPORT

## The impact of patient heterogeneity and socioeconomic factors on abatacept retention in rheumatoid arthritis across nine European countries

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## ABSTRACT

**Background:** There are substantial differences in accessibility to biological disease modifying antirheumatic drugs (bDMARDs) across countries. The objective of this study was to analyse the impact of patient demographics, disease characteristics and gross domestic product (GDP) on abatacept (ABA) retention in patients with rheumatoid arthritis (RA) treated in clinical practice.

**Methods:** Data from nine European observational RA cohorts of patients treated with ABA were pooled. Kaplan-Meier analysis was used to compare drug retention across registries. Specific causes of drug retention were investigated using competing risks multivariate Cox regression.

**Results:** A total of 3961 patients treated with ABA, with 6188 patient-years of follow-up, were included. Patients in the different national registries had similar demographic features, but varied in baseline disease characteristics. ABA drug retention differed between countries, with median drug retention rates ranging from 1.2 to more than 6 years. The differences in drug retention were marginally explained by disparities in disease characteristics, while the national GDP per capita was strongly associated with drug retention (correlation coefficient  $-0.74$ ;  $p=0.02$ ).

**Conclusions:** Patient characteristics at ABA initiation vary across Europe, probably reflecting differences in eligibility criteria and prescription patterns. However, the difference in ABA drug retention between countries was not primarily explained by disparities in patient characteristics. Lower ABA retention was observed in countries with a more liberal access to bDMARDs and higher GDP. National differences need to be accounted for when pooling data on treatment with bDMARDs from various countries.

## INTRODUCTION

To increase statistical power when analysing effectiveness and safety of biological disease modifying antirheumatic drugs (bDMARDs) in rheumatoid arthritis (RA), investigators

## Key messages

## What is already known on this subject?

Recent literature has highlighted important differences in access to b-DMARDs across Europe.

## What might this study add?

The results of this study illustrate the impact of inequity of access to b-DMARD on drug effectiveness.

## How might this impact on clinical practice?

While pooling data from various registries is useful to increase statistical power when analysing safety and effectiveness of antirheumatic drugs, our findings suggest that national differences should be accounted for when combining data from various countries.

have recently started pooling data from several national registries.<sup>1</sup> This procedure is particularly useful when studying rare outcomes or rare exposures. Substantial differences exist across countries in terms of accessibility to biological agents.<sup>2–4</sup> The impact of these differences on RA outcomes is still largely unknown.

In recent years, a number of bDMARDs have been introduced for the treatment of RA. Abatacept (ABA), a selective T-cell costimulation inhibitor, has been shown in randomised controlled clinical trials to be effective in patients with RA and active disease despite treatment with methotrexate,<sup>5 6</sup> as well as in those with an inadequate response to antitumour necrosis factor (TNF) therapy.<sup>7</sup> ABA was approved in the European Union (EU) for the treatment of RA in 2007, and subsequently reimbursed in most EU countries in 2008. European league against rheumatism recommendations for management of RA have included ABA as second-line and, recently, as a first-line bDMARD.<sup>8 9</sup>



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Drug retention is a measure of overall drug effectiveness, integrating safety and efficacy. Major differences in drug retention of bDMARDs across observational studies have been reported.<sup>10</sup> The aim of the present analysis was to acquire new insights regarding national differences in ABA use and effectiveness across European countries, using pooled data from European registries to build a pan-European ABA database. Our hypothesis was that differences in the case mix and also factors reflecting differences in the healthcare system in various countries affect drug retention.

## METHODS

### Study design

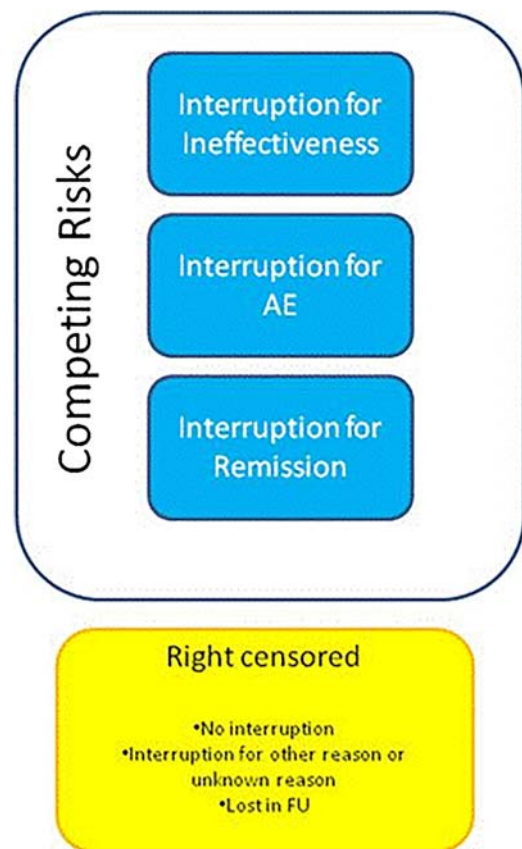
Nine RA national registries have contributed to this collaborative analysis: ARTIS (Sweden), ATTRA (Czech Republic), BIOBADASER (Spain), DANBIO (Denmark), GISEA (Italy), NOR-DMARD (Norway), ORA (France), SCQM (Switzerland) and REUMA.PT (Portugal). These registries and their methodologies have been described in detail elsewhere.<sup>11 12</sup> Inclusion criteria for this analysis were a diagnosis of RA, and registered initiation of ABA treatment before the end of 2013.

Approval for this project from the relevant research ethics committees have been obtained by all the included registries. Informed consent for inclusion in the registry and use of anonymous data for this type of analysis in research projects has been obtained from all patients. The study's primary outcome was ABA drug retention. Secondary outcomes were ABA interruption for ineffectiveness, adverse events (AE) and remission, respectively, as defined by the treating rheumatologists. Time to discontinuation was defined as the time between ABA initiation and last administration plus 1 month (dispensation interval).

### Statistical analysis

We analysed patient demographics and disease characteristics at treatment initiation using standard descriptive statistics. Patients lost to follow-up or patients who stopped therapy due to reasons deemed unrelated to ABA (pregnancy, relocation or other) were right censored.

We computed ABA drug retention rate using a Kaplan–Meier (K-M) estimator and compared differences across registries using the log-rank test. To correct for potential confounding factors, we conducted multivariate Cox regression, adjusting for patient demographics (age, gender), disease characteristics (rheumatoid factor (RF), DAS28 at baseline, disease duration) and treatment characteristics (number of prior bDMARDs, calendar year of ABA initiation). We also explored the countries' gross domestic product (GDP<sup>13</sup>) as an explanatory variable for differences in drug retention rate. For secondary outcomes, three-specific causes of interruption were considered, namely ineffectiveness, AE and remission. Since K-M is not applicable in the presence of competing risks, we performed a cumulative incidence function (CIF) analysis



**Figure 1** Competing risks structure for ABA treatment interruption. *Note:* Individuals who have the competing event remain in the risk set until their 'potential' censoring time (ABA, abatacept; AE, adverse events; FU, follow-up).

to model the specific causes of ABA discontinuation using a Fine and Gray (F-G) regression.<sup>14 15</sup> Figure 1 summarises the structure of our competing risk framework for ABA discontinuation.

## RESULTS

### Patient characteristics

A total of 3961 patients treated with ABA contributed with 6188 patient-years of follow-up (median of 1.1 years/patient; IQR 0.5–2.4). Baseline characteristics for each national registry are reported in table 1. Overall, the registries had fairly similar demographics, but greater heterogeneity existed for RA disease characteristics: functional disability ranged from a mean health assessment questionnaire (HAQ) score of 1.0 (SCQM) to 1.7 (BIOBADASER), and disease-activity measured by DAS28 ranged from mean 4.1 (SCQM) to 5.7 (ATTRA). There were also major differences in the number of prior synthetic DMARDs (median ranging from 1 (SCQM, ARTIS, REUMA.PT) to 4 (ATTRA, DANBIO)) and the number of prior bDMARDs before ABA initiation (median ranging from 1 (SCQM, DANBIO, GISEA) to 2 (others)).

### Primary outcome: drug retention rate analysis

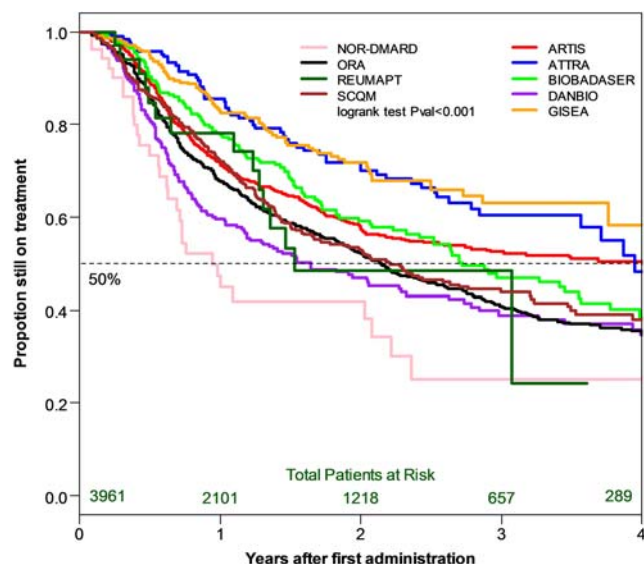
The survival curves depicted in figure 2 show major heterogeneity in ABA retention rate across countries. Despite

**Table 1** Baseline characteristics at ABA initiation across nine European registries

Registers	Follow-up (pt-years)	Follow-up /pt	Male %	Age (years)	RF %	Anti-CCP %	Disease duration (years)	HAQ*	DAS28	BMI (kg/m <sup>2</sup> )	CRP (mg/L)	ESR (mm/h)	sDMARDs (n)	bDMARDs (n)	Median year of ABA initiation
Combined(3961 pts)	6188	1.1(0.5–2.4)	19.4	57.3±13.0	76.8	68.3	11.3±8.1	1.3±0.7	5.0±1.3	26.0±5.1	22.2±34.2	31.6±24.4	2.4±1.8	1.8±1.4	2009
ARTIS(1019 pts)	1615	1.0(0.5–2.1)	20.7	58.6±12.4	–	–	9.6±3.9	1.3±0.7	5.1±1.3	24.8±1.5	19.6±26.5	30.4±23.0	1.6±1.0	1.9±1.3	2011
ATTRA(215 pts)	356	1.2(0.6–2.6)	20.9	50.1±12.5	70.1	74.7	11.2±7.7	1.5±0.5	5.7±1.1	25.5±4.9	25.7±29.3	38.3±24.3	3.7±1.7	–	2010
BIOBADASER (283 pts)	507	1.5(0.7–2.5)	18.4	56.6±13.1	83.7	60	12.1±8.4	1.7±0.7	5.1±1.6	–	18.1±26.0	33.6±27.7	–	2.3±1.9	2010
DANBIO(315 pts)	437	0.8(0.4–2.0)	19.0	56.0±12.5	84.3	59.3	11.4±9.6	1.4±0.7	4.9±1.2	26.3±5.6	18.3±26.2	–	4.3±2.2	1.4±1.1	2010
GISEA(375 pts)	503	1.1(0.5–2.0)	13.3	56.5±12.5	73.6	81.7	10.6±8.4	1.4±0.8	5.0±1.1	25.8±5.0	39.0±66.0	34.4±23.4	2.5±1.5	1.4±1.0	2010
NOR-DMARD(52 pts)	54	0.7(0.4–1.1)	11.5	51.3±12.5	59.6	48.9	14.8±9.7	0.9±0.5	5.4±1.1	24.0±4.1	24.2±34.2	36.4±28.1	3.2±1.5	1 (1–2)	2009
ORA(1019 pts)	1832	1.4(0.6–2.9)	20.8	58.2±13.6	71.2	69.7	13.6±9.5	1.2±0.7	5.3±1.2	–	25.1±32.8	35.5±27.7	3.1±1.8	2.3±1.3	2008
REUMA.PT (37 pts)	48	1.2(0.5–1.6)	13.5	59.0±14.1	57.1	51.6	12.3±8.3	1.6±0.7	5.5±1.6	27.2±5.7	15.4±15.4	40.6±24.8	1.6±1.1	2.0±1.3	2010
SCQM(646 pts)	835	0.9(0.4–1.7)	20.0	57.8±12.5	72.6	67.0	10.0±8.9	1.0±0.7	4.1±1.4	26.0±5.1	12.0±16.2	23.4±19.7	1.0±1.1	1.2±1.2	2010
													1 (0–2)	1 (0–2)	

\*Values are means±SD and median [IQR], unless otherwise noted.

ABA, abatacept; BMI, body mass index; bDMARDs, biological disease modifying antirheumatic drugs; CCP, CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; pts, patients; RF, rheumatoid factor; sDMARDs, synthetic DMARDs.



**Figure 2** Abatacept drug retention across European countries.

adjusting for differences in demographics (age, gender), disease and treatment characteristics (number of past biotherapies, disease duration, RF, DAS28), and calendar effect, this heterogeneity remained, suggesting that differences in retention could be due to alternative factors. Our exploratory analysis led us to focus on national socio-economic factors, which have been suggested to be relevant in this context.<sup>2-4</sup> We found a significant negative association between the national GDP per capita and drug retention rate (Pearson correlation coefficient  $-0.74$ ,  $p=0.021$ ). Adjusted for demographics and disease characteristics, drug retention rate was shorter in countries with higher GDP per capita (table 2). When categorising countries according to the GDP, the median drug retention time for countries with a GDP per capita (in purchasing power parity) above the median European GDP of €30 000 (ORA, DANBIO, ARTIS, SCQM and NOR-DMARD; group 1) was 2.2 (2.1 to 2.5) years versus 5.1 (3.9 to 5.1) years for countries with GDPs below €30 000 per capita (BIOBADASER, ATTRA, REUMA.PT and GISEA; group 2;

figure 3). After adjustment for all potential confounders (see above), the HR (95% CI) for discontinuation for group 1 versus group 2 was 1.50 (1.32 to 1.71). The HRs (95% CI) for each national registry with ARTIS as the reference ranged from 0.63 (0.42 to 0.95) for ATTRA to 1.98 (1.29 to 3.05) for NOR-DMARD (table 2). Results were similar in analyses restricted to patients with one previous bDMARD (data not shown). The factors included in the multivariate model were: number of past bDMARDs (HR 1.43 (1.18 to 1.74), 1.54 (1.27 to 1.86), 1.67 (1.36 to 2.04) and 1.83 (1.48 to 2.28), for 1, 2, 3 and  $\geq 4$  past bDMARDs, respectively, with no prior bDMARDs as reference), disease activity at baseline (HR (DAS28) 1.07 per unit (1.03 to 1.13)) and presence of RF (HR 0.77 (0.67 to 0.88)).

### Specific causes of ABA interruption

When focusing on the specific causes of ABA interruption separately, 77% of interruptions were attributed to inefficacy, 22% to AE and only 2% to remission.

The estimated CIFs show that the probability of interruption due to inefficacy was 8% within 6 months, 21% within 1 year and 34% within 2 years. The probability of interruption due to AEs was 4% within 6 months, 6% within 1 year and 9% within 2 years. As for the overall drug retention rates, large differences between countries were observed. The highest risk of interruption for inefficacy and for AEs was seen in the French (ORA), the Swedish (ARTIS) and the Swiss (SCQM) registries (figure 4A, B).

The multivariate analysis pointed out the number of prior bDMARDs, younger age, DAS28 at baseline and negative RF as significant risk factors for discontinuation due to ineffectiveness, whereas, older age and number of prior bDMARDs were significant predictors of discontinuation for AE.

### DISCUSSION

In this study, we demonstrated large differences in ABA drug retention across European countries. These differences were not primarily explained by patient or disease characteristics, but were associated with national economic features. This may reflect differences in treatment

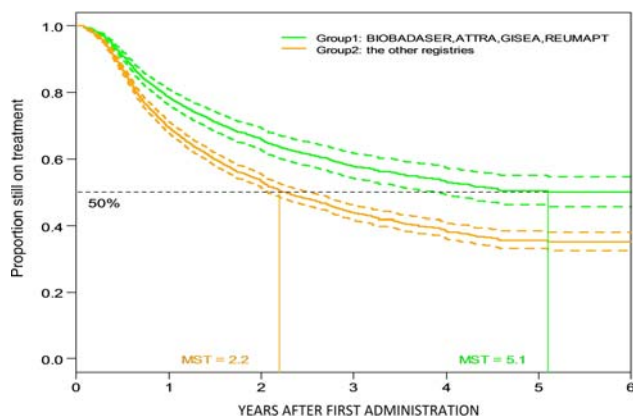
**Table 2** Association between HRs and adjusted MST

Registry	Patients at risk	Events	MST (CI)* (in year)	HR±SE (95% CI)†	GDP per capita (US\$; rank)
ARTIS	1019	366	3.2 (3.4-na)	1.00 (Ref)	37 775 (3)
ATTRA	215	57	>6.0	0.63±0.21 (0.42 to 0.95)	24 986 (8)
BIOBADASER	283	119	3.6 (2.5-na)	0.96±0.15 (0.72 to 1.28)	29 651 (6)
DANBIO	315	149	1.8 (1.4 to 2.4)	1.50±0.14 (1.14 to 1.98)	36 763 (4)
GISEA	375	77	>6.0	0.64±0.17 (0.46 to 0.89)	29 417 (7)
NOR-DMARD	52	30	1.2 (0.9 to 2.3)	1.98±0.22 (1.29 to 3.05)	52 238 (1)
ORA	1019	543	2.5 (2.1 to 3.1)	1.18±0.12 (0.92 to 1.5)	34 092 (5)
REUMA.PT	37	15	3.0 (1.6-na)	1.03±0.31 (0.56 to 1.89)	23 113 (9)
SCQM	646	236	2.0 (1.6 to 2.4)	1.40±0.13 (1.09 to 1.80)	41 765 (2)

\*MST in years adjusted for potential confounding factors.

†Adjusted HR.

ABA, abatacept; GDP, gross domestic product; MST, median survival time; na, not applicable.



**Figure 3** Abatacept drug retention according to gross domestic product (GDP) groups (Crude Cox regression). *Note:* Group 1 puts together the European countries with the higher GDPs (ORA, DANBIO, ARTIS, SCQM and NOR-DMARD) while group 2 includes the others, that is, GDPs per capita greater than €30 000 (BIOBADASER, ATTRA, REUMAPT and GISEA).

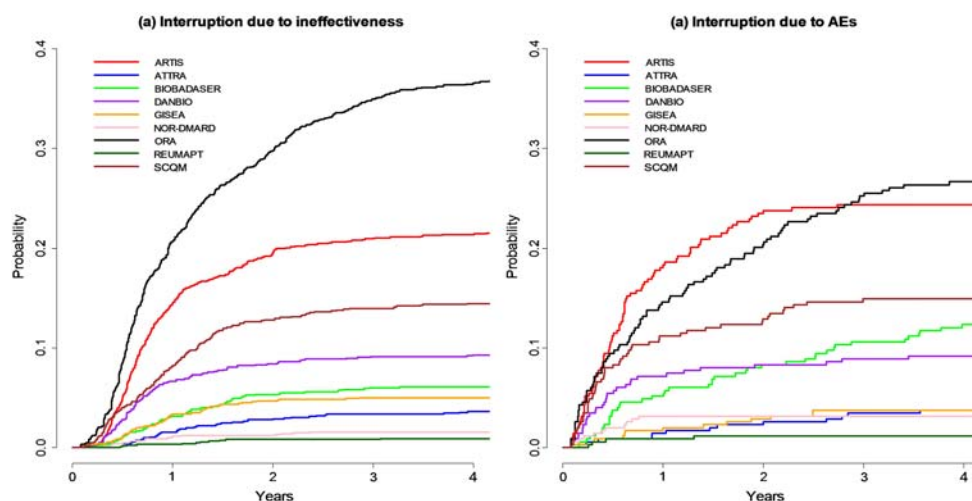
strategies, driven by disparities in the healthcare systems of the contributing countries.

Recent literature has highlighted important differences in access to bDMARDs across Europe, but the impact of these differences on drug effectiveness remains largely unknown. For instance, Putrik *et al*<sup>2</sup> stressed that Eastern and Central Europe tend to have less access to bDMARDs. In the present study, patients with RA included in the ATTRA register from the Czech Republic, along with those in the Italian GISEA register, had substantially longer drug retention rates compared with patients from other countries in this study, in particular those in the Norwegian NOR-DMARD register and the SCQM register in Switzerland. The inverse association between GDP and drug retention could reflect a consequence of the inequity of access to bDMARDs across Europe. Interestingly, we found that patient and

disease characteristics were not the driving force behind differences in drug retention. We can only hypothesise how socioeconomic features may affect drug retention. It could have to do with regulatory issues relating to access to bDMARDs (cost of drugs, administrative burdens, reimbursement concerns, physician's right to prescribe bDMARDs), local guidelines, local physician preferences<sup>16</sup> or other factors affecting the ease of bDMARD switching, patient and physician's expectations, or the number of available treatment choices. The fact that the drug investigated in this study was ABA rather than a TNF inhibitor may have amplified differences across countries, as ABA is mostly used as a second-line bDMARD. Heterogeneity between countries was also observed in the specific causes of interruption. For instance, France and Sweden not only recorded the highest probability to stop the treatment for ineffectiveness, but also for AEs. While the results of this study may not be applicable to other countries, our results are consistent with another prospective international cohort study of patients treated with ABA, which found similar national trends and predictors of drug retention.<sup>17 18</sup>

The inclusion of several large national registries from different parts of Europe is a major strength of this study. The availability of data on baseline characteristics from patients treated in clinical practice and followed according to standard procedures in national registers is crucial for this type of analysis.

It is important to keep in mind that many individual socioeconomic professional factors (ie, education level, individual income) may also account for some variations in drug retention. Unfortunately, we had no uniform measure for individual socioeconomic factors across registries, which is an important limitation of our investigation. Moreover, missing data of specific variables is a common limitation in observational studies. RF was missing in approximately one-third of patients, however, the results of the analysis did not change qualitatively when these patients were excluded compared to analyses



**Figure 4** Cumulative incidence functions (CIF). *Note:* The CIF represents the probability that an event *j* has occurred by the time *t*.

where statistical imputations were used to impute the missing covariate, suggesting that missing RF status was not significantly influencing the results. Furthermore, the results for the specific reasons of ABA interruption should be interpreted with caution, as data on AE or remission as a reason for discontinuing ABA were not captured in the same manner in all registries. Furthermore, selection bias, such as differences in recruitment into registries, and bias related to unmeasured confounders, cannot be excluded.

While heterogeneity in access to bDMARDs across Europe is a fact, the results of this study illustrate a potential impact of access inequity on drug retention. These findings beg the question on how access to therapy may influence the use of these medications. Do rheumatologists unconsciously discontinue a bDMARD more often and sooner when alternative bDMARDs are more easily available? While pooling data from national registries is useful to assess safety and drug retention, our findings suggest that results from analyses of pooled data should be interpreted with caution. It is not enough to correct for patient and disease characteristics, but national differences should be accounted for when combining data from various countries for real-life studies of treatment outcomes.

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**Ethics approval** Local and National Ethical registries (9 countries).

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**Data sharing statement** No additional data are available.

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# The impact of patient heterogeneity and socioeconomic factors on abatacept retention in rheumatoid arthritis across nine European countries

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