Efficacy and prognostic factors of treatment retention with intravenous abatacept for rheumatoid arthritis: 24-month results from an international, prospective, real-world study

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Supplementary material

Methods

Prognostic factors of intravenous abatacept retention

Data concerning potential prognostic factors, including known risk factors and clinically relevant variables, were collected at abatacept initiation. Continuous and categorized variables were considered in this analysis. Categorizations were based on validated cut-offs when available, or on clinical expertise of the ACTION Scientific Committee, published literature, or descriptive statistics such as medians or quartiles. All potential prognostic factors tested in the univariate analysis and the corresponding categorizations are presented in Table S1. In the main multivariate model, no imputation for missing data was applied and therefore patients with complete data who were identified in the multivariate analysis were included in the final multivariate model. Three sensitivity analyses were performed to account for missing data in the covariates.

Table S1. Potential prognostic factors tested in the univariate analysis.

Variable	Categories	Comment
Sociodemographics		
Age	Mean (SD) *<65 years* ≥65 years	European Medicines Agency categories to define elderly (used in abatacept SmPC)[1]
BMI	Mean (SD) *<25 kg/m²* 25–<30 kg/m² 30–<35 kg/m² ≥35 kg/m²	Validated categories[2]
Sex	*Male* Female	

Country	*Germany*	
	Canada	
	Greece	
	Italy	
	Austria	
	Netherlands	
	Czech Republic	
Disease characteristics		
Disease duration	Mean (SD)	
	≤2 years	
	>2–5 years	Usual categories used in literature for established RA
	>5–10 years	
	>10 years	
Tender joint count (28)	Mean (SD)	
Swollen joint count (28)	Mean (SD)	
HAQ-DI	*<1.50*	Cut-off=median
	≥1.50	
CRP	*<4 mg/L*	
	4–<10 mg/L	Cut-off=quartiles
	10–<26 mg/L	
	≥26 mg/L	
	Not done[a]	
ESR	*<17 mm/hour*	
	17–<30 mm/hour	Cut-off=quartiles
	30–<51 mm/hour	
	≥51 mm/hour	
	Not done[a]	
Patient Global Assessment	*<70 mm*	Cut-off=median
	≥70 mm	

	Not done[a]	
Physician Global Assessment	*<65 mm*	
	≥65 mm	Cut-off=median
	Not done[a]	
Patient pain	*<70 mm*	
	≥70 mm	Cut-off=median
	Not done[a]	
DAS28 (ESR, otherwise CRP)	*DAS28 <2.6 or DAS28 ≤3.2*	
	MDAS	Validated categories[3]
	HDAS	
	Not done[a]	
CDAI (calculated)	*≤22 (Remission to MDAS)*	
	>22 (HDAS)	Validated categories[4]
	Missing[a]	
Radiographic erosion	*No*	
	Yes	
RF status[b]	*Negative*	
	Positive	
	Not available[a]	
Anti-CCP status	*Negative*	
	Positive	
	Not available[a]	
RF and anti-CCP double positivity	*No*	
	Yes	
	Not available[a]	
Comorbidities		
Cardiac disorders	*No*	Agreed by Scientific Committee, based on MedDRA coding
	Yes	
COPD	*No*	

	Yes	
Diabetes mellitus	*No*	
	Yes	
Tobacco use	*No*	
	Yes	
Infections	*No*	
	Yes	
Previous treatments		
Number of prior cDMARDs	*0–3*	Cut-off used in literature, confirmed by Scientific Committee
	>3	
Number of prior anti-TNFs	≥*2*	Cut-off used in literature, confirmed by Scientific Committee
	<2	
Type of biologic agent before abatacept initiation	*Other MoA*	
	Anti-TNF agent	
RTX as last treatment before abatacept initiation	*No*	
	Yes	
Reason for discontinuation of last biologic	*Intolerance*	
	Primary inefficacy	
	Secondary inefficacy	
	Major improvement + other reasons	
Concomitant treatments		
Abatacept treatment pattern at initiation	*Monotherapy*	Agreed by Scientific Committee
	Combination with MTX (+/-cDMARDs)	
	Combination with other cDMARDs	
Corticosteroid treatment pattern at abatacept initiation (versus before initiation)	*No corticosteroids or cessation of corticosteroids*	Agreed by Scientific Committee
	Continuous use of corticosteroids	
	Introduction of corticosteroids	

Category in italics is the reference category.

[a]Only in sensitivity analyses 1 and 3. In sensitivity analysis 2, original data reported as 'not done' were set as missing and then imputed.

[b]As reported by the investigator.

BMI: body mass index; CCP: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; cDMARD: conventional disease-modifying antirheumatic drug; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire–Disability Index; HDAS: high disease activity state; MedDRA: Medical Dictionary for Regulatory Activities; MDAS: moderate disease activity state; MoA: mode of action; MTX: methotrexate; RA: rheumatoid arthritis; RF: rheumatoid factor; RTX: rituximab; SD: standard deviation; SMPC: summary of product characteristics; TNF: tumour necrosis factor.

The imputation model was based on multiple imputation using chained equations (MICE) using the IVEware add-in program in SAS® software (Statistical Analysis System Institute Inc., Cary, NC, USA). The imputations were obtained by fitting a sequence of regression models and drawing values from the corresponding predictive distributions.[5] This pragmatic approach generates imputations as model-fitted values and does not rely on the underlying distribution of variables. Missing values were imputed 20 times to create 20 complete datasets which were independently analysed. The stability of descriptive analysis was checked across the original dataset (with missing data) and the 20 complete datasets. This method of imputation was used in the three sensitivity analyses.

In two sensitivity analyses, the final multivariate model was defined using a decision rule based on the p-value for covariates; selection was as follows: multivariate models were conducted on the 20 generated datasets using the stepwise descending selection process where covariates with p-value >0.1 were not retained in the model. The final list of prognostic factors used to build the final multivariate model included all covariates which were selected in at least 75% (*i.e*. 15/20) models. Using this final list of prognostic factors, one multivariate model for each complete dataset was run and estimated hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were aggregated with the MIANALYZE SAS® procedure to give final adjusted estimates.

In the first sensitivity analysis, imputation was applied for the covariates where the information 'Not done' was originally collected in the case report form. During the imputation process, the missing parameter was first imputed as 'Done' versus 'Not done' and then values were imputed in the first case only. Finally, in the complete datasets, the category 'Not done' was considered as a modality for the considered parameter. This approach is rational in the context of the analysis of an outcome such as retention, which is a therapeutic decision including multiple aspects extending beyond the intrinsic effect of the treatment. One can consider the information that the parameter was not measured as

informative data that may help us to understand the therapeutic decision as well as any other possible value for the considered parameter.

However, to have a complete overview and to assess the impact of this assumption, a second sensitivity analysis was conducted in which the category 'Not done' was considered to be non-informative and therefore set as missing. After imputation of missing data, the complete datasets no longer contained the category 'Not done'.

In the third sensitivity analysis, an *a priori* list of covariates was defined, based on clinical experience and literature, and is presented in Table S2. Compared with the other sensitivity analyses, there was no selection of covariates. The multivariate model was run in each of the 20 complete datasets and estimated HRs and corresponding 95% CIs were aggregated to give final adjusted estimates.

Table S2. Covariates used in the third sensitivity analysis.

Sociodemographics
• Country
• Age
• Sex
• BMI
Disease characteristics
• Disease duration
• DAS28 (ESR, otherwise CRP) at baseline
• RF status
• Anti-CCP status
Comorbidities at initiation
• Infections
• COPD
• Tobacco use
• Diabetes
• Cardiac disorder
Number of previous anti-TNF agents
Monotherapy versus combination

BMI: body mass index; CCP: cyclic citrullinated peptide; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; TNF: tumour necrosis factor.

Table S3 presents a summary of all analyses conducted, identifying the different assumptions considered.

Table S3. Summary of analyses.

	Analysis population	**Imputation of missing data?**	**Method of imputation of missing data**	**'Not done'= category?**	**Step of covariates selection to build final multivariate model?**	**Method of covariates selection?**	**Final analysis population**	**Outcome**
Main analysis	• Patients with ≥1 previous biologic agent • Enrolled in countries with a sufficient number of patients (Belgium and Denmark not considered) ➔ n=995	No	Not applicable	Yes	Yes	Univariate analysis then stepwise descending selection	Patients with information available for all covariates selected in the final multivariate model ➔ n=916/995	List of prognostic factors with adjusted HR and 95% CI
Sensitivity 1		**Yes (MICE)**	Imputation of missing information in covariates (Parameter 'Done'/'Not done' ➔ if 'Done', value imputed)	Yes	Yes	Covariates selection as significant at $p \leq 0.10$ in at least 75% of multivariate models run in the 20 complete	Same as defined in 2nd column ➔ n=995	

						datasets		
Sensitivity 2			**Original information 'Not done' set as missing then value imputed**	**No**	Yes	Covariates selection as significant at $p \leq 0.10$ in at least 75% of multivariate models run in the 20 complete datasets		
Sensitivity 3			Imputation of missing information in covariates (Parameter 'Done'/'Not done' ➔ if 'Done', value imputed)	Yes	**No**	***A priori* list of covariates (clinical experience, literature)**		

CI: confidence interval; HR: hazard ratio; MICE: multiple imputation using chained equations.

Results

Subgroup analysis: adherence and European League Against Rheumatism (EULAR) response by body mass index (BMI) grouping

A similar percentage of patients were adherent to abatacept in each BMI group: 285/344 (82.8%) for underweight/normal, 245/308 (79.5%) for overweight, 130/153 (85.0%) for obese class I and 69/82 (84.1%) for obese class II/III patients. In total, 43/343 (12.5%) patients with underweight/normal BMI and 73/539 (13.5%) patients with BMI ≥25 kg/m^2 received one or two additional abatacept infusions.

At 24 months, a good or moderate EULAR response, based on 28-joint Disease Activity Score (erythrocyte sedimentation rate or C-reactive protein) was achieved in a similar proportion of patients in each BMI group: 96/117 (82.1%) for underweight/normal, 74/96 (77.1%) for overweight, 35/44 (79.5%) for obese class I and 19/22 (86.4%) for obese class II/III.

Figure S1. Univariate analysis of abatacept retention (main analysis).

Analysis includes patients who enrolled in Austria, Canada, Czech Republic, Germany, Greece, Italy, and Netherlands who previously received ≥1 biologic agent.

CCP: cyclic citrullinated peptide; CI: confidence interval; CS: corticosteroid; csDMARD: conventional synthetic disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; HR: hazard ratio; MoA: mode of action; MTX: methotrexate; RF: rheumatoid factor; TNF: tumour necrosis factor.

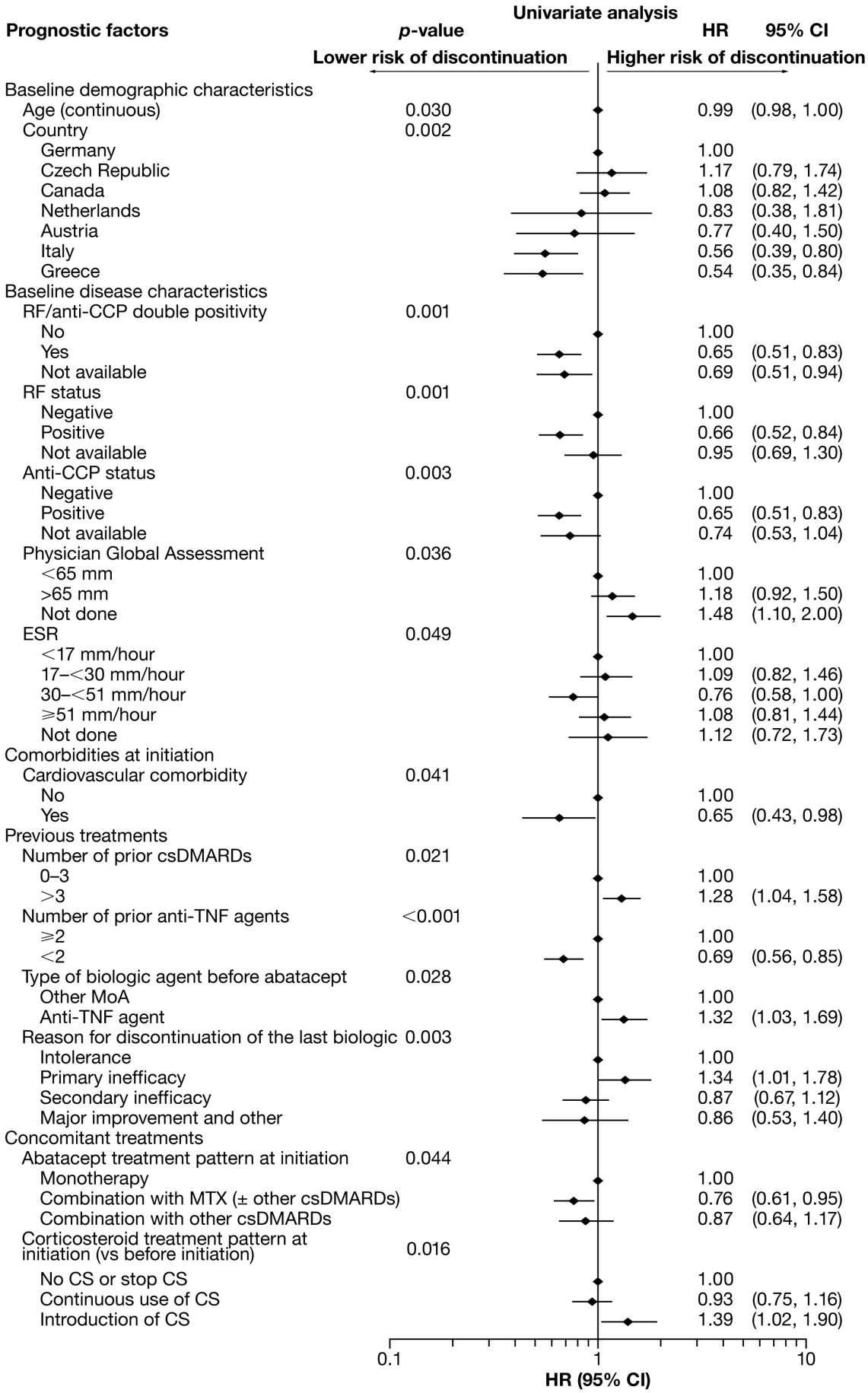
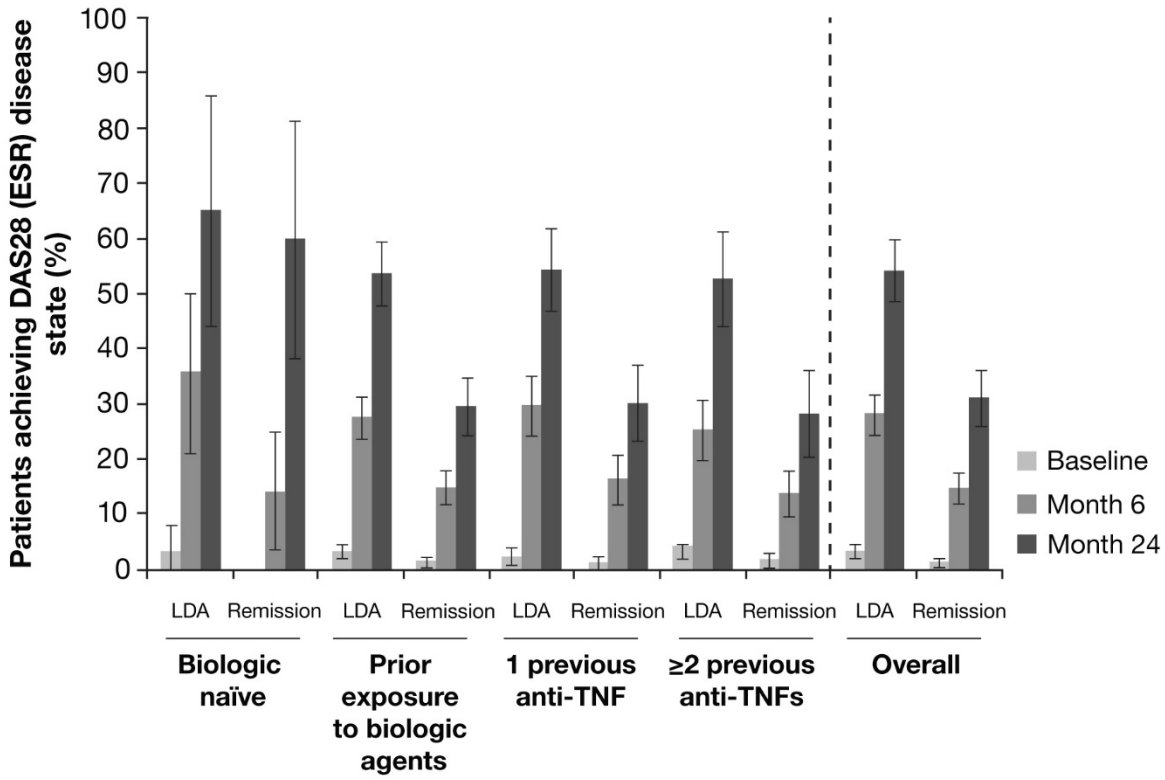

Univariate analysis
Prognostic factors
p-value
HR
95% CI
Lower risk of discontinuation
Higher risk of discontinuation
Baseline demographic characteristics
Age (continuous) 0.030 0.99 (0.98, 1.00)
Country 0.002
Germany 1.00
Czech Republic 1.17 (0.79, 1.74)
Canada 1.08 (0.82, 1.42)
Netherlands 0.83 (0.38, 1.81)
Austria 0.77 (0.40, 1.50)
Italy 0.56 (0.39, 0.80)
Greece 0.54 (0.35, 0.84)
Baseline disease characteristics
RF/anti-CCP double positivity 0.001
No 1.00
Yes 0.65 (0.51, 0.83)
Not available 0.69 (0.51, 0.94)
RF status 0.001
Negative 1.00
Positive 0.66 (0.52, 0.84)
Not available 0.95 (0.69, 1.30)
Anti-CCP status 0.003
Negative 1.00
Positive 0.65 (0.51, 0.83)
Not available 0.74 (0.53, 1.04)
Physician Global Assessment 0.036
<65 mm 1.00
>65 mm 1.18 (0.92, 1.50)
Not done 1.48 (1.10, 2.00)
ESR 0.049
<17 mm/hour 1.00
17–<30 mm/hour 1.09 (0.82, 1.46)
30–<51 mm/hour 0.76 (0.58, 1.00)
⩾51 mm/hour 1.08 (0.81, 1.44)
Not done 1.12 (0.72, 1.73)
Comorbidities at initiation
Cardiovascular comorbidity 0.041
No 1.00
Yes 0.65 (0.43, 0.98)
Previous treatments
Number of prior csDMARDs 0.021
0–3 1.00
>3 1.28 (1.04, 1.58)
Number of prior anti-TNF agents <0.001
⩾2 1.00
<2 0.69 (0.56, 0.85)
Type of biologic agent before abatacept 0.028
Other MoA 1.00
Anti-TNF agent 1.32 (1.03, 1.69)
Reason for discontinuation of the last biologic 0.003
Intolerance 1.00
Primary inefficacy 1.34 (1.01, 1.78)
Secondary inefficacy 0.87 (0.67, 1.12)
Major improvement and other 0.86 (0.53, 1.40)
Concomitant treatments
Abatacept treatment pattern at initiation 0.044
Monotherapy 1.00
Combination with MTX (± other csDMARDs) 0.76 (0.61, 0.95)
Combination with other csDMARDs 0.87 (0.64, 1.17)
Corticosteroid treatment pattern at initiation (vs before initiation) 0.016
No CS or stop CS 1.00
Continuous use of CS 0.93 (0.75, 1.16)
Introduction of CS 1.39 (1.02, 1.90)
0.1
1
10
HR (95% CI)

Figure S2. Percentage of patients achieving various efficacy measures over 24 months (a) DAS28 (ESR) (collected)*, (b) DAS28 (CRP) (collected)*, (c) CDAI†, (d) Boolean remission‡. n represents the number of patients with data available. *DAS28 (ESR) and (CRP) LDA if DAS28 ≤3.2 and remission if DAS28 <2.6. †CDAI remission if CDAI ≤2.8 and LDA if CDAI ≤10. ‡Boolean remission if tender joint count ≤1, swollen joint count ≤1, CRP ≤1 mg/dL and Patient Global Assessment ≤1.

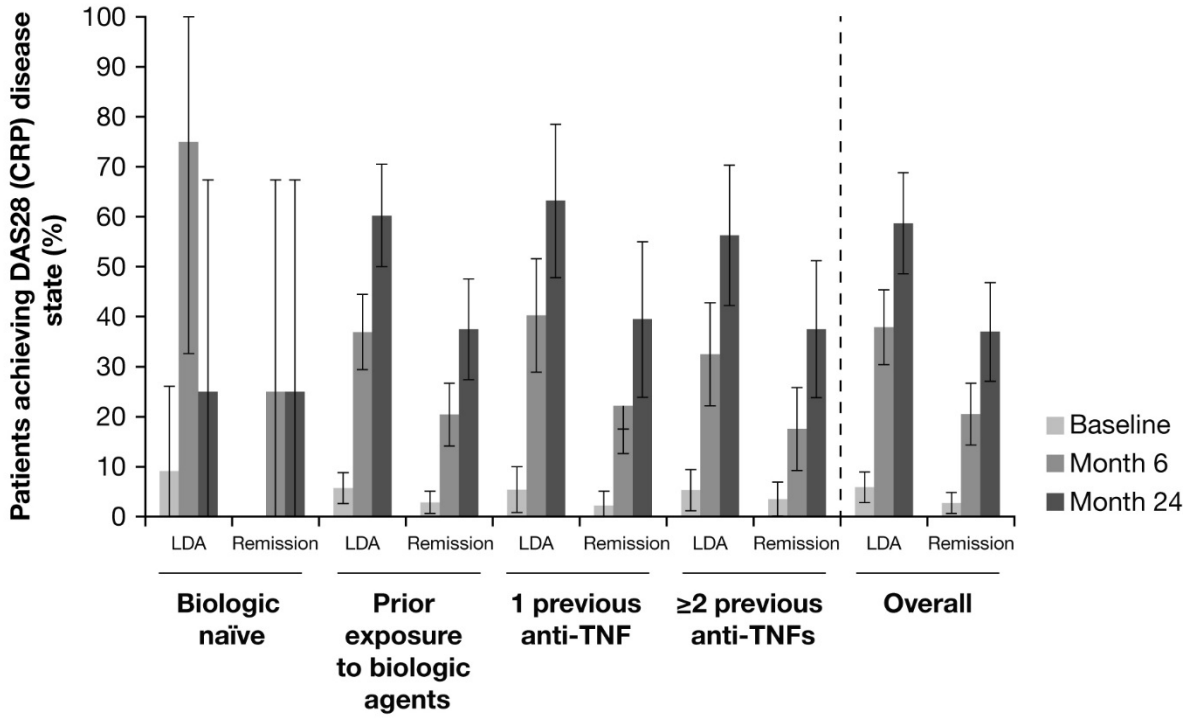
CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; LDA: low disease activity.

A



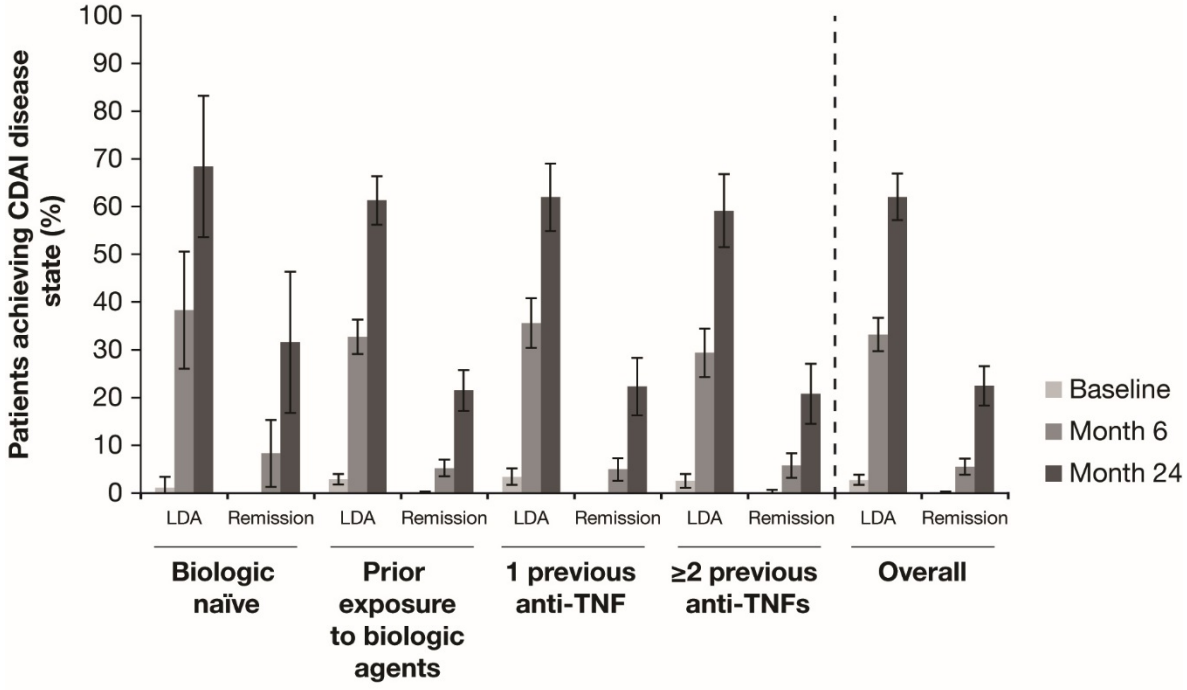
	Baseline (n)	Month 6 (n)	Month 24 (n)
Biologic naïve	59	42	20
Prior exposure to biologic agents	711	538	298
1 previous anti-TNF	345	269	169
≥2 previous anti-TNFs	357	261	127
Overall	770	580	318

B



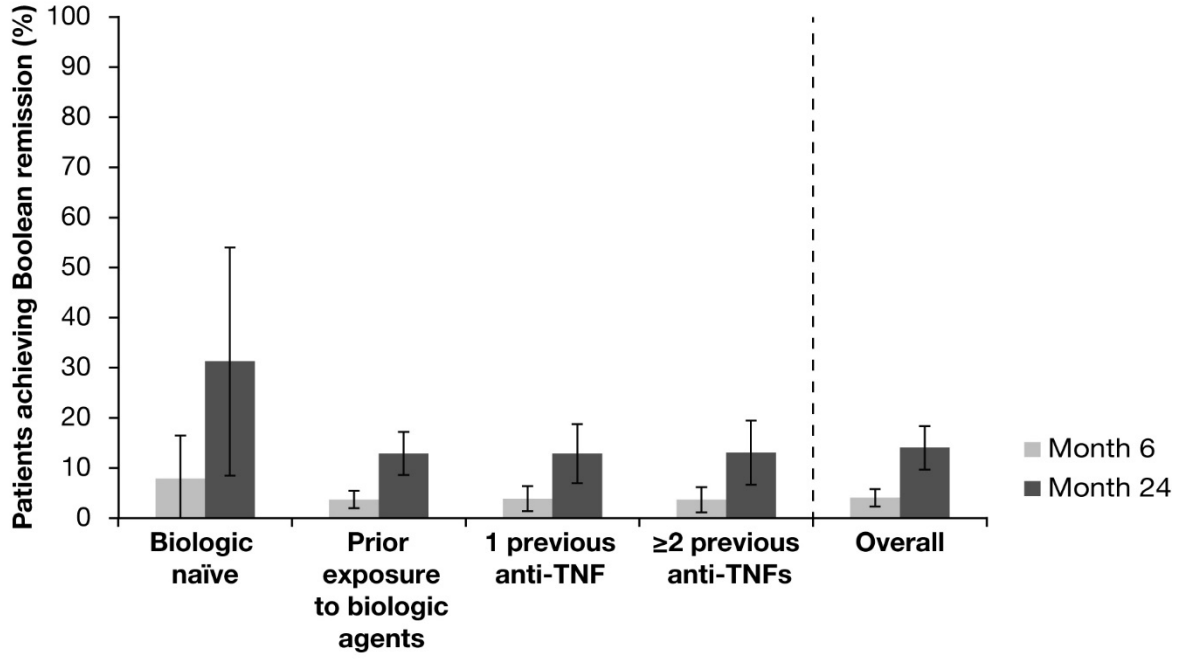
	Baseline (n)	Month 6 (n)	Month 24 (n)
Biologic naïve	11	4	4
Prior exposure to biologic agents	211	157	88
1 previous anti-TNF	93	72	38
≥2 previous anti-TNFs	114	80	48
Overall	222	161	92

C



	Baseline (n)	Month 6 (n)	Month 24 (n)
Biologic naïve	88	60	38
Prior exposure to biologic agents	858	648	349
1 previous anti-TNF	410	323	184
≥2 previous anti-TNFs	433	313	159
Overall	946	708	387

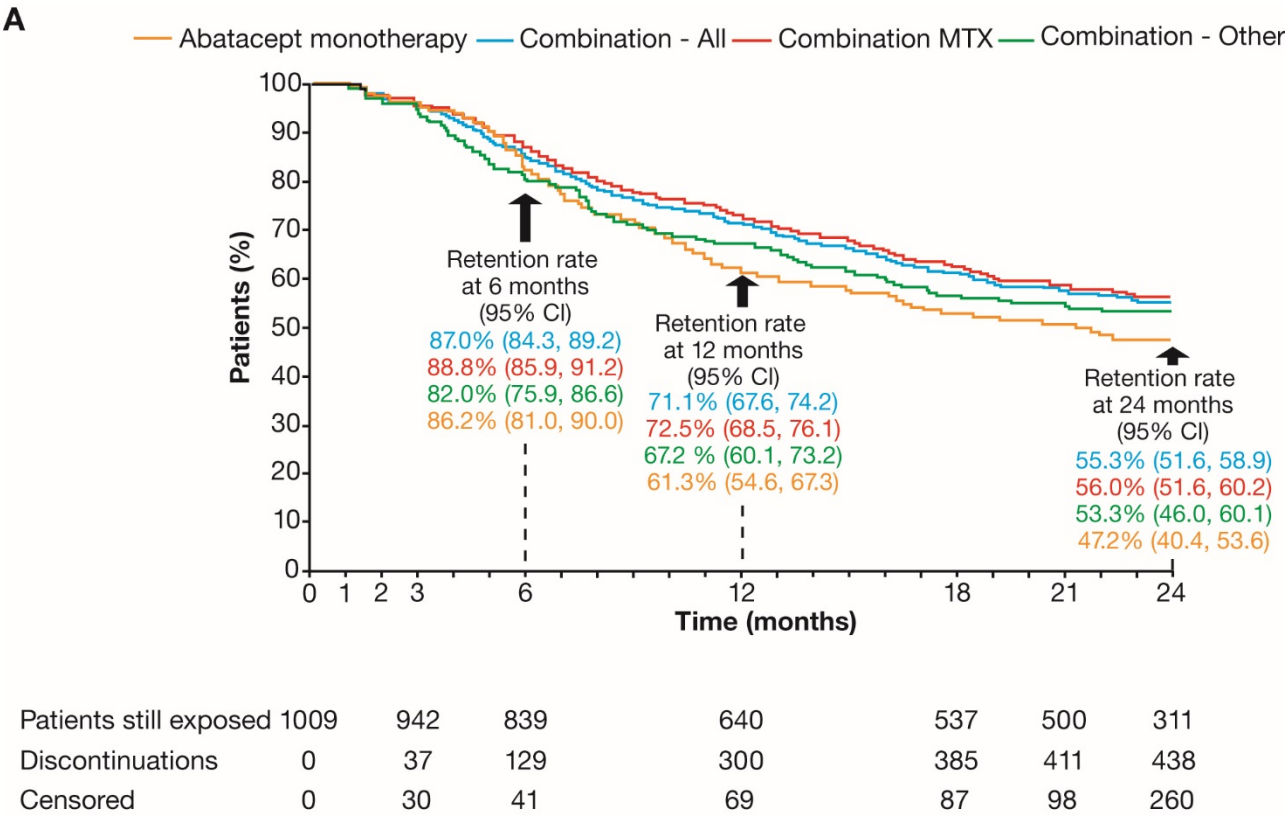
D



	Month 6 (n)	Month 24 (n)
Biologic naïve	38	16
Prior exposure to biologic agents	455	233
1 previous anti-TNF	229	124
≥2 previous anti-TNFs	217	107
Overall	493	249

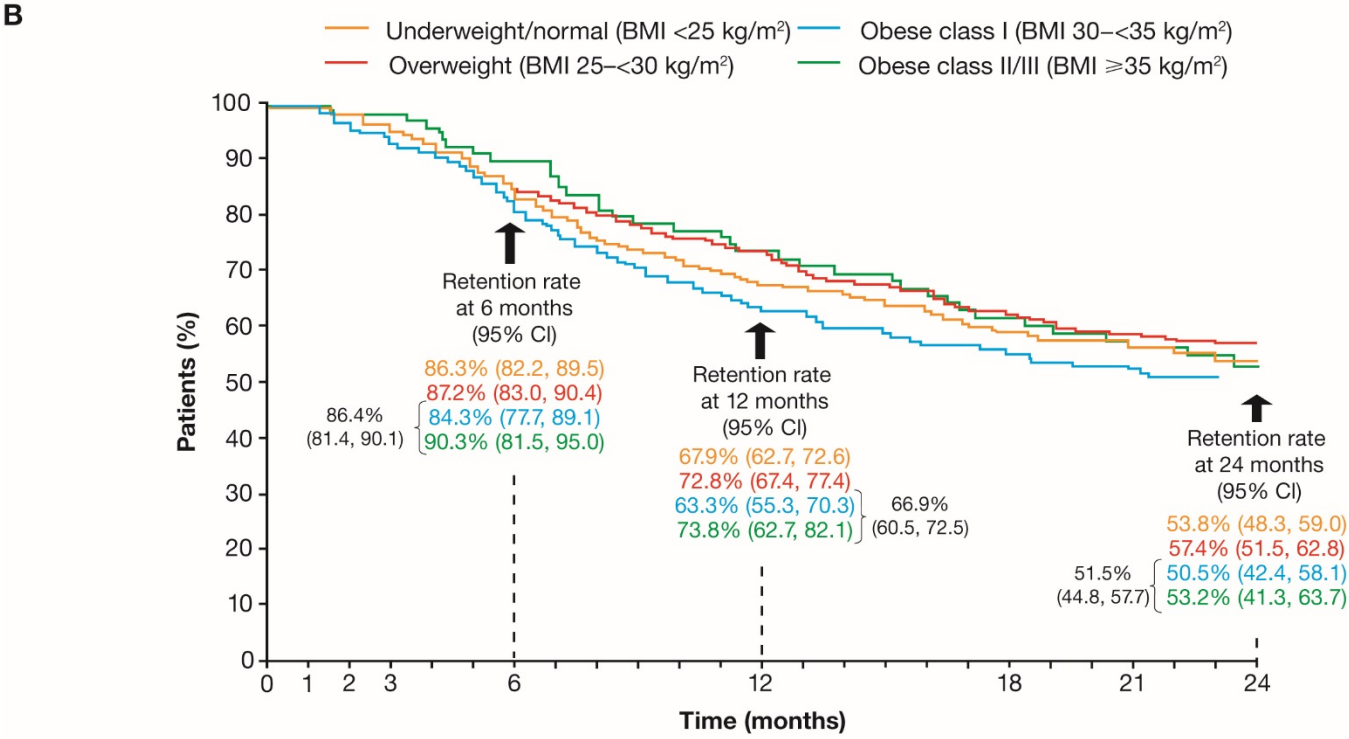
Fig. S3. Crude patient retention rates (95% CI) estimated by Kaplan–Meier over 24 months (a) by concomitant treatment at abatacept initiation in patients with prior exposure to ≥1 biologic agent; (b) by BMI group in patients with prior exposure to ≥1 biologic agent. If abatacept was discontinued, exposure to abatacept was defined as the time between the date of the first abatacept infusion and the date of the last abatacept infusion, plus 30 days. Censoring of patients not reporting discontinuation was performed using date of death, date of last contact or date of last follow-up visit.

BMI: body mass index; CI: confidence intervals; MTX: methotrexate.



Patients still exposed	1009	942	839	640	537	500	311
Discontinuations	0	37	129	300	385	411	438
Censored	0	30	41	69	87	98	260

B



Patients still exposed	936	873	775	595	504	469	291
Discontinuations	0	34	121	273	347	372	396
Censored	0	29	40	68	85	95	249

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