A window of opportunity for csDMARD in rheumatoid arthritis and its positive impact on 10-year outcomes: results from the ESPOIR cohort

Supplementary materials

Supplementary material 1: table of dose quotients (DoseQ) for conventional and biological disease-modifying anti-rheumatic drugs

csDMARDS		
Drug	**Posology**	**Dose quotient**
methotrexate	2.5 mg/1 week	0.125
	5 mg/1 week	0.25
	7.5 to 12.5 mg/1 week	0.5
	15 mg/1 week	0.75
	17.5 to 22.5 mg/1 week	1
	25 mg/1 week	1.25
leflunomide	10 mg/2 days	0.25
	10 mg/1 day	0.5
	20 mg/1 day	1
sulfasalazine	0.5 g/1 day	0.125
	1 g/1 day	0.25
	1.5 g/1 day	0.375
	2 g/1 day	0.5
	2.5 g/1 day	0.625
	3 g/1 day	0.75
	4 to 6 g/1 day	1
bDMARDs		
Drug	**Posology**	**Dose quotient**
adalimumab	40 mg/6 weeks	0.125
	40 mg/4 weeks	0.25
	40 mg/3 weeks	0.75
	40 mg/2 weeks	1
	80 mg/1 month	1
	40 mg/1 week	1.5
certolizumab	200 mg/2 weeks	1
etanercept	50 mg/1 month	0.125
	25 mg/2 weeks	0.125
	50 mg/3 weeks	0.25
	50 mg/2 weeks	0.5
	25 mg/1 week	0.5
	50 mg/1 week	1
	25 mg/3 days	1
	75 mg/1 week	1.5
golimumab	50 mg/1 month	1
infliximab	3 mg/kg/infusion	1

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	5 mg/kg/infusion	1.6
rituximab	500 mg/1 infusion	0.5
	1000 mg/1 infusion	1
tocilizumab	162 mg/2 weeks (SC)	0.5
	any posology/6 weeks (IV)	0.75
	162 mg/1 week (SC)	1
	any posology/4 weeks (IV)	1
abatacept	125 mg/2 weeks (SC)	0.5
	any posology/6 weeks (IV)	0.75
	125 mg/1 week (SC)	1
	any posology/4 weeks (IV)	1

Footnote: bDMARD: biologic disease-modifying anti-rheumatic drugs; csDMARD: conventional synthetic disease-modifying anti-rheumatic drugs ; IV: intravenous; SC: subcutaneous

Supplementary Material 2: description of the exposure to csDMARD and bDMARD in the FavOut study group, in the AbsSDP study group and in patients not considered in the analyses:

- **For FavOut:**

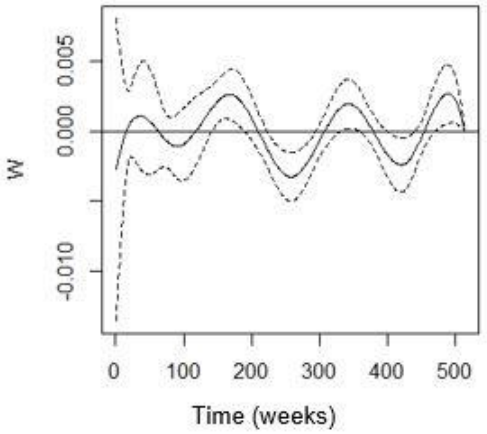
	FavOut study population (N=418)	**Population not considered in the analysis (N=395)**
csDMARD	374 (89.5%)	243 (61.5%)
bDMARD	150 (35.9%)	54 (13.7%)
csDMARD only	227 (54.3%)	190 (48.1%)
bDMARD only	3 (0.7%)	1 (0.3%)
csDMARD and bDMARD	147 (35.2%)	53 (13.4%)
No DMARD	41 (9.8%)	151 (38.2%)

- **For AbsSDP:**

	AbsSDP study population (N=343)	**Population not considered in the analysis (N=470)**
csDMARD	300 (87.5%)	317 (67.5%)
bDMARD	118 (34.4%)	86 (18.3%)
csDMARD only	185 (53.9%)	232 (49.4%)
bDMARD only	3 (0.9%)	1 (0.2%)
csDMARD and bDMARD	115 (33.5%)	85 (18.1%)
No DMARD	40 (11.7%)	152 (32.3%)

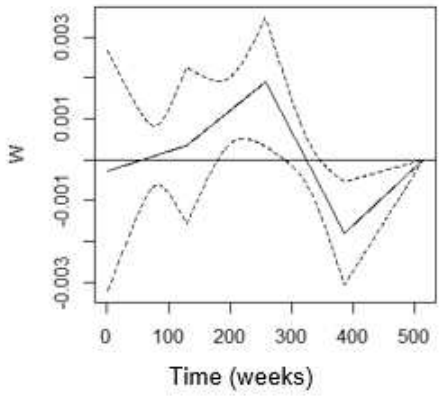
Supplementary Material 3: univariate weighted-cumulative exposure (WCE) models for favorable outcome (FavOut) at 10 years:

a) For conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (5 knots, degree 3, time window 520 weeks, AIC=712.96)



Profile tested	Reference	OR (95%CI)
1 DoseQ for the last 12 months	No csDMARD for the last 120 months	1.01 (0.91-1.12)
1 DoseQ for the last 24 months	No csDMARD for the last 120 months	0.98 (0.89-1.08)
1 DoseQ for the last 60 months	No csDMARD for the last 120 months	1.02 (0.94-1.11)
1 DoseQ for the last 120 months	No csDMARD for the last 120 months	1.0 0.92-1.10)

b) For biologic disease-modifying anti-rheumatic drugs (bDMARDs) (3 knots, degree 1, time window 520 weeks , AIC=316.10)



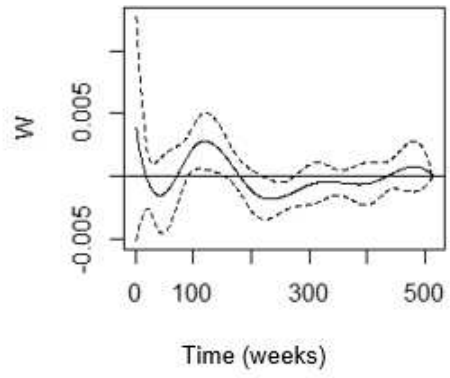
Profile tested	Reference	OR (95%CI)
1 DoseQ for the last 12 months	No bDMARDs for the last 120 months	0.99 (0.89-1.10)
1 DoseQ for the last 24 months	No bDMARDs for the last 120 months	1.00 (0.88-1.13)
1 DoseQ for the last 60 months	No bDMARDs for the last 120 months	***1.16 (1.03-1.32)***
1 DoseQ for the last 120 months	No bDMARDs for the last 120 months	1.04 (0.88-1.22)

Supplementary Material 4: sensitivity analysis of the WCE model for FavOut, restricting the analysis to patients having initiated a DMARD in the first year of follow-up

N=343 patients (82.1%) initiated a DMARD in the first 12 months of the disease course/follow-up in the ESPOIR cohort. FavOut occurred in 155 (45.2%) of this new study population.

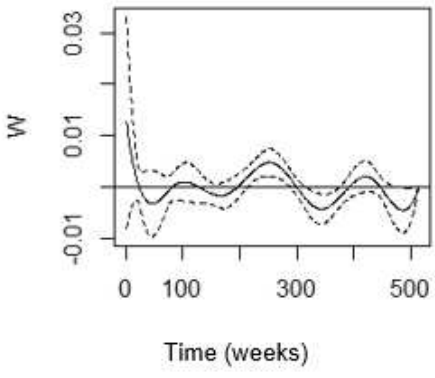
- Univariate WCE analysis

For csDMARD (5 knots, degree 3, time window of 520 weeks, AIC=646.67):



Profil tested	Reference	OR (95%CI)
1 DoseQ in the last 12 months	No csDMARDs	1.04 (0.94-1.17)
1 DoseQ in the last 24 months	No csDMARDs	1.05 (0.94-1.16)
1 DoseQ in the last 60 months	No csDMARDs	1.06 (0.97-1.17)
1 DoseQ in the last 120 months	No csDMARDs	0.99 (0.89-1.11)

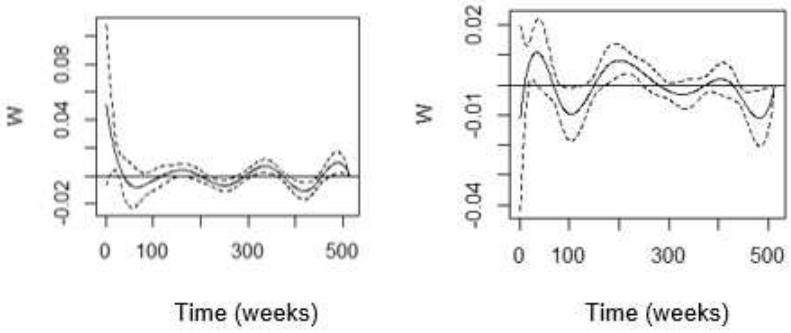
For bDMARD (5 knots, degree 3, time window 520 weeks, AIC=291.82):



Profil tested	Reference	OR (95%CI)
1 DoseQ in the last 12 months	No bDMARDs	1.06 (0.90-1.24)
1 DoseQ in the last 24 months	No bDMARDs	1.02 (0.90-1.17)
1 DoseQ in the last 60 months	No bDMARDs	***1.17 (1.02-1.35)***
1 DoseQ in the last 120 months	No bDMARDs	0.91 (0.74-1.13)

- **Multivariate analysis: WCE combined model:**

AIC=228.62



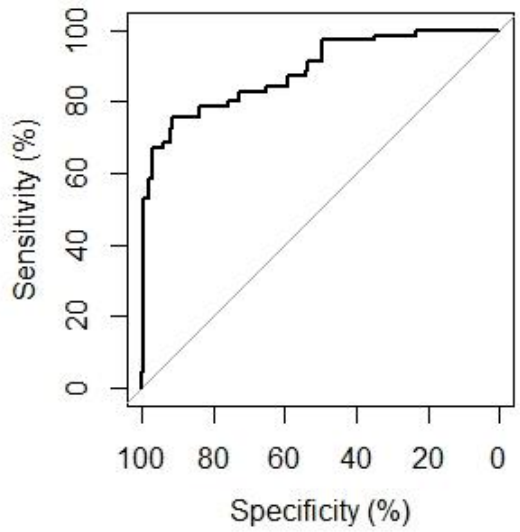
csDMARD ***bDMARD***

Exposure tested	**Reference**	**OR (95%CI)**
Window of Opportunity: interest of csDMARDs early initiation (bDMARD excluded)		
csDMARD delayed after week 6	csDMARD started at inclusion (month 0)	***0.99 (0.98-1.00)***
csDMARD delayed after month 3	csDMARD started at inclusion (month 0)	***0.95 (0.93-0.99)***
csDMARD delayed after month 6	csDMARD started at inclusion (month 0)	***0.86 (0.77-0.97)***
csDMARD delayed after month 12	csDMARD started at inclusion (month 0)	***0.71 (0.52-0.96)***
Window of Opportunity: interest of bDMARDs early initiation (in combination with csDMARD)		
bDMARD after 3 months of follow-up	csDMARD started at inclusion (month 0)	0.86 (0.59-1.26)
bDMARD after 6 months of follow-up	csDMARD started at inclusion (month 0)	0.96 (0.70-1.31)
bDMARD after 12 months of follow-up	csDMARD started at inclusion (month 0)	1.28 (0.98-1.68)
bDMARD after 24 months of follow-up	csDMARD started at inclusion (month 0)	***1.44 (1.08-1.94)***
bDMARD after 36 months of follow-up	csDMARD started at inclusion (month 0)	***1.37 (1.01-1.87)***
bDMARD after 48 months of follow-up	csDMARD started at inclusion (month 0)	***1.60 (1.25-2.04)***
bDMARD after 60 months of follow-up	csDMARD started at inclusion (month 0)	***1.61 (1.28-2.03)***

Variable	**OR (95% CI)**
Age	0.99 (0.94-1.05)
HAQ-DI	0.06 (0.01-3.88)
DAS28-ESR	***2.27 (1.38-3.88)***
Mean total vSHS	0.96 (0.87-1.04)
Patient's global assessment	0.98 (0.95-1.01)
Fatigue	0.99 (0.98-1.02)
Low income	0.87 (0.24-2.85)

In this model, early csDMARD initiation is associated with an increased odd of FavOut at 10 years (compared with delayed initiation, even of only 6 weeks), whereas bDMARD initiation is associated with an increased odd of FavOut after 2 years of follow-up, compared with patients having initiated early a csDMARD.

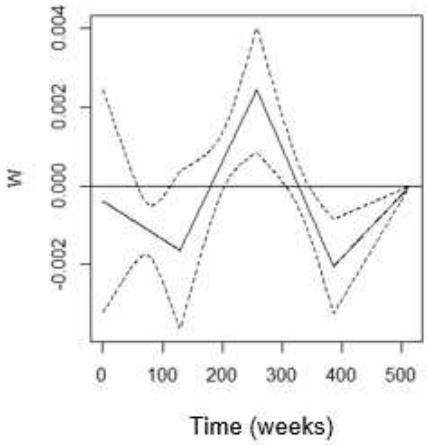
ROC curve:



AUC = 0.89 (0.84-0.93)

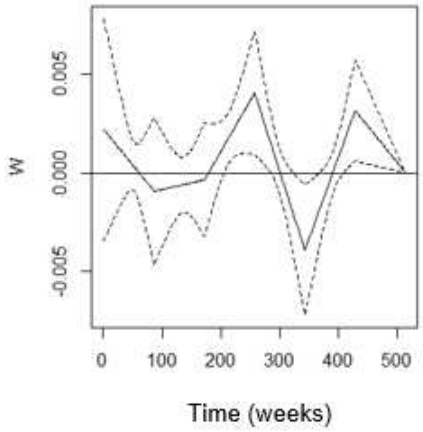
Supplementary Material 5: univariate weighted-cumulative exposure (WCE) models for absence of structural damage progression (SDP) at 10 years:

a) For conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (3 knots, 1 degree, time window 520 weeks, AIC=499.69)



Profile tested	Reference	OR (95%CI)
1 DoseQ for the last 12 months	No csDMARD for the last 120 months	0.97 (0.87-1.07)
1 DoseQ for the last 24 months	No csDMARD for the last 120 months	0.91 (0.81-1.02)
1 DoseQ for the last 60 months	No csDMARD for the last 120 months	0.93 (0.84-1.01)
1 DoseQ for the last 120 months	No csDMARD for the last 120 months	***0.83 (0.74-0.93)***

b) For biologic disease-modifying anti-rheumatic drugs (bDMARDs) (5 knots, 1 degree, time window 520 weeks, AIC=263.91)



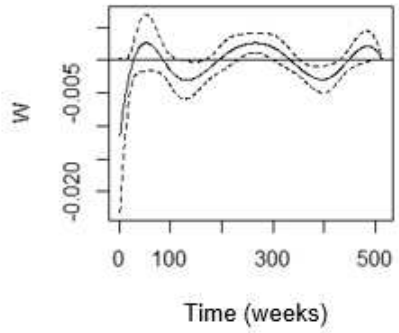
Profile tested	Reference	OR (95%CI)
1 DoseQ for the last 12 months	No bDMARDs for the last 120 months	1.07 (0.91-1.25)
1 DoseQ for the last 24 months	No bDMARDs for the last 120 months	1.04 (0.92-1.18)
1 DoseQ for the last 60 months	No bDMARDs for the last 120 months	***1.17 (1.02-1.36)***
1 DoseQ for the last 120 months	No bDMARDs for the last 120 months	***1.31 (1.08-1.58)***

Supplementary Material 6: sensitivity analysis of the WCE model for FavOut, restricting the analysis to patients having initiated a DMARD in the first year of follow-up

N=271 patients (79.0%) initiated a DMARD in the first 12 months of the disease course/follow-up in the ESPOIR cohort. Among those patients, AbsSDP was observed in N=189 (69.74%) patients.

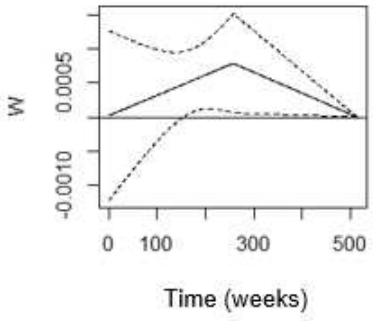
- Univariate WCE analysis

For csDMARD (4 knots, degree 3, time window of 520 weeks, AIC=459.35):



Profil tested	Reference	OR (95%CI)
1 DoseQ in the last 12 months	No csDMARDs	0.91 (0.80-1.04)
1 DoseQ in the last 24 months	No csDMARDs	0.95 (0.82-1.09)
1 DoseQ in the last 60 months	No csDMARDs	***0.87 (0.77-0.98)***
1 DoseQ in the last 120 months	No csDMARDs	0.88 (0.78-1.02)

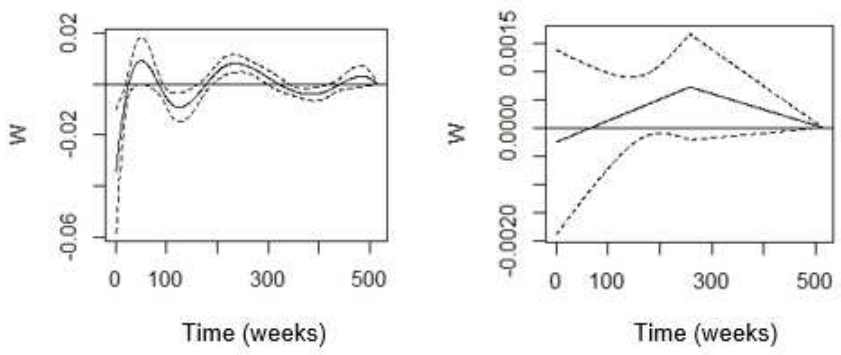
For bDMARD (1 knot, degree 1, time window of 520 weeks, AIC=238.98):



Profil tested	Reference	OR (95%CI)
1 DoseQ in the last 12 months	No bDMARDs	1.00 (0.95-1.06)
1 DoseQ in the last 24 months	No bDMARDs	1.02 (0.92-1.12)
1 DoseQ in the last 60 months	No bDMARDs	1.11 (0.96-1.28)
1 DoseQ in the last 120 months	No bDMARDs	***1.23 (1.03-1.47)***

- Multivariate analysis: WCE combined model

AIC=251.65

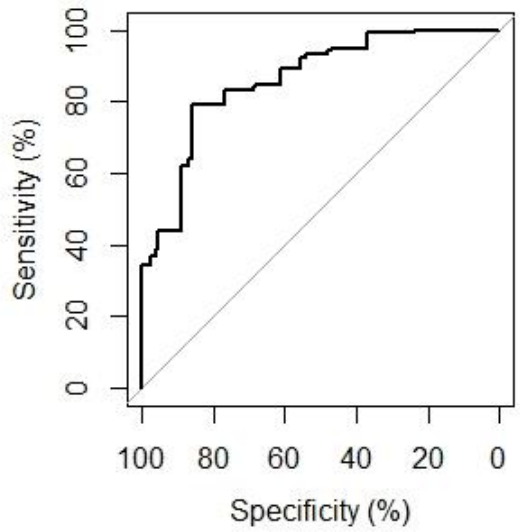


Window of Opportunity: interest of csDMARDs early initiation (bDMARD excluded)		
csDMARD delayed after week 6	csDMARD started at inclusion (month 0)	1.00 (0.99-1.01)
csDMARD delayed after month 3	csDMARD started at inclusion (month 0)	**0.99 (0.97-1.00)**
csDMARD delayed after month 6	csDMARD started at inclusion (month 0)	**0.96 (0.91-0.99)**
csDMARD delayed after month 12	csDMARD started at inclusion (month 0)	**0.89 (0.77-0.98)**
Window of Opportunity: interest of bDMARDs early initiation (in combination with csDMARD)		
bDMARD after 3 months of follow-up	csDMARD started at inclusion (month 0)	1.16 (0.94-1.44)
bDMARD after 6 months of follow-up	csDMARD started at inclusion (month 0)	1.16 (0.94-1.43)
bDMARD after 12 months of follow-up	csDMARD started at inclusion (month 0)	1.15 (0.94-1.43)
bDMARD after 24 months of follow-up	csDMARD started at inclusion (month 0)	1.14 (0.94-1.40)
bDMARD after 36 months of follow-up	csDMARD started at inclusion (month 0)	1.13 (0.93-1.36)
bDMARD after 48 months of follow-up	csDMARD started at inclusion (month 0)	1.10 (0.92-1.31)
bDMARD after 60 months of follow-up	csDMARD started at inclusion (month 0)	1.06 (0.89-1.26)

Variables	**OR (IC95%)**
Mean total vSHS	***0.88 (0.77-0.97)***
CRP	***0.97 (0.96-0.99)***
ACPA positivity	***0.19 (0.08-0.41)***
Tender joint count (/28)	1.05 (0.99-1.12)

In this model, odds of AbsSDP were associated with early initiation of csDMARDs (as soon as inclusion in the ESPOIR cohort) as compared with initiation at 3, 6 or 12 months of follow-up. Additionally, combined treatment with csDMARDs (initiated early) and bDMARDs (with different delays of bDMARD initiation) versus early initiated csDMARDs monotherapy had no significant benefit for AbsSDP. The predictive performance of this new model was good, with AUC=0.86 (0.82-0.92); for comparison, in the previous analysis, AUC was worth 0.87 (95% CI, 0.83 to 0.92).

ROC curve:



AUC=0.86 (0.82-0.92)