SUPPLEMENTARY MATERIAL

Title

Methotrexate Maintenance after Initiation of Biological or Targeted Synthetic DMARDs in Rheumatoid Arthritis: Results from the 2-year Longitudinal Prospective Non-Interventional STRATEGE2 Study

Author Details

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Supplementary Table S1. Reasons driving the decision to discontinue MTX treatment

Reasons for MTX Discontinuation	Inclusion visit	M12 visit	M24 visit
Adverse event, *n* (%)		10 (35.7)	14 (35.9)
Participant decision, *n* (%)	3 (75.0)	11 (39.3)	13 (33.3)
Attempting to conceive, *n* (%)	1 (25.0)	2 (7.1)	4 (10.3)
Remission, *n* (%)			2 (5.1)
Adverse event AND participant decision, *n* (%)		2 (7.1)	2 (5.1)
Participant decision AND another reason, *n* (%)			1 (2.6)
Another reason, *n* (%)		3 (10.7)	3 (7.7)

Abbreviations: *M12*, study visit 12 months after b/tsDMARD initiation; *M24*, study visit 24 months after b/tsDMARD initiation; *MTX*, methotrexate.

Supplementary Table S2. Adverse events leading to MTX discontinuation

List of AE	MTX dose and route of administration	AE Severity	Severity criteria	Resolution of AE	AE resolved after MTX discontinuation
Liver disturbance (transaminases x5)	17.5 mg/week Subcutaneous	Moderate	Non-severe	Full recovery without sequelae	Yes
Nausea	22.5 mg/week Subcutaneous	Mild	Non-severe	Full recovery without sequelae	Yes
Diarrhoea	20 mg/week Oral	Moderate	Non-severe	Not resolved	No
Alopecia	20 mg/week Subcutaneous	Moderate	Non-severe	Full recovery without sequelae	Yes
Visual disturbances	20 mg/week Subcutaneous	Moderate	Non-severe	Full recovery without sequelae	Yes
Dry morning cough	20 mg/week Subcutaneous	Moderate	Non-severe	Full recovery without sequelae	Yes
Nausea	20 mg/week Oral	Moderate	Non-severe	Full recovery without sequelae	Yes
Impaired liver function	10 mg/week Oral	Moderate	Other medically significant condition	Not resolved	Unknown
Allergic reaction	10 mg/week Oral	Moderate	Non-severe	Unknown	Unknown
Leukoneutropenia	10 mg/week Oral	Moderate	Other medically significant condition	Full recovery without sequelae	Yes
Neutropenia	10 mg/week Oral	Moderate	Other medically significant condition	Ongoing recovery	Unknown

Supplementary Table S3. Univariate logistic regression: reasons driving the decision to maintain MTX at M24

Logistic regression (univariate) - M24, *N*=157					
Factor	***N***	**Maintenance of MTX for the first two years after b/tsDMARD initiation**	***P* type III**	**OR [95% CI]**	***P* versus Reference**
Factors related to the participant					
b/tsDMARD monotherapy or combination therapy	Missing (*N*=1)				
	Monotherapy (*N*=80) (Reference)	33.8%	0.952		
	Combination therapy (*N*=76)	34.2%		1.02 [0.53; 1.98]	0.952
Alternative disability index (score HAQ-DI without adjustment)	Missing (*N*=22)				
	Quantitative analysis (*N*=135)		0.285	1.36 [0.78; 2.37]	
Corticosteroids at inclusion	Missing (*N*=1)				
	No (*N*=76)	35.5%	0.816	1.08 [0.56; 2.09]	0.816
	Yes (*N*=80) (Reference)	33.8%			
CQR19 Total score < 80% / ≥ 80%	Missing (*N*=21)				
	< 80 percent (*N*=84) (Reference)	31.0%	0.982		
	≥ 80 percent (*N*=52)	30.8%		0.99 [0.47; 2.10]	0.982
Age [years]	Quantitative analysis (*N*=157)		0.020	1.03 [1.00; 1.06]	
MTX injection done by (at inclusion):	Missing (*N*=2)				
	Patient (*N*=126)	33.3%	0.638	0.82 [0.35; 1.89]	0.638
	Someone else (*N*=29) (Reference)	37.9%			
Body mass index >= 30 kg/m^2	Missing (*N*=5)				
	Yes (*N*=24)	29.2%	0.480	0.71 [0.27; 1.84]	0.480
	No (*N*=128) (Reference)	36.7%			
Professional status	Working (*N*=77) (Reference)	31.2%	0.404		
	Other (*N*=80)	37.5%		1.32 [0.68; 2.57]	0.404
Nicotine consumption	Current smoker (*N*=31) (Reference)	22.6%	0.127		
	Former smoker / No-smoker (*N*=126)	37.3%		2.04 [0.82; 5.10]	0.127
At least one medical history or comorbidities	Yes (*N*=82)	37.8%	0.348	1.37 [0.71; 2.67]	0.348
	No (*N*=75) (Reference)	30.7%			
Rheumatoid factor	Missing (*N*=9)				
	Positive (*N*=112)	33.0%	0.734	0.87 [0.40; 1.92]	0.734
	Negative (*N*=36) (Reference)	36.1%			

Logistic regression (univariate) - M24, *N*=157					
Factor	***N***	**Maintenance of MTX for the first two years after b/tsDMARD initiation**	***P* type III**	**OR [95% CI]**	***P* versus Reference**
Anti-CCP rate	Missing (*N*=8)				
	Positive (*N*=108)	33.3%	0.925	0.96 [0.45; 2.06]	0.925
	Negative (*N*=41) (Reference)	34.1%			
Diagnosis history (years)	Quantitative analysis (*N*=157)		0.398	1.02 [0.98; 1.06]	
Presence of radiologic signs	Missing (*N*=1)				
	Yes (*N*=74)	36.5%	0.641	1.17 [0.60; 2.27]	0.641
	No (*N*=82) (Reference)	32.9%			
Number of swollen joints	Missing (*N*=3)				
	Quantitative analysis (*N*=154)		0.642	1.02 [0.94; 1.10]	
Rate of CRP (mg/L)	Missing (*N*=2)				
	Quantitative analysis (*N*=155)		0.401	1.00 [1.00; 1.01]	
Evaluation of disease activity by the participant (visual analogue scale 100–mm)	Missing (*N*=7)				
	Quantitative analysis (*N*=150)		0.117	1.01 [1.00; 1.03]	
Did you participate to a global program of therapeutic re-education?	Missing (*N*=23)				
	Yes (*N*=26)	30.8%	0.944	0.97 [0.38; 2.44]	0.944
	No (*N*=108) (Reference)	31.5%			

Logistic regression (univariate) - M24, *N*=157					
Factor	***N***	**Maintenance of MTX for the first two years after b/tsDMARD initiation**	***P* type III**	**OR [95% CI]**	***P* versus Reference**
Factors related to the practitioner					
Type of practice	Hospital-based practice (*N*=110)	40.9%	0.010	2.92 [1.29; 6.64]	0.010
	Hospital-based and private practice (*N*=47) (Reference)	19.1%			
Who send the patient to you?	Rheumatologist (*N*=48) (Reference)	35.4%	0.858		
	Other (*N*=109)	33.9%		0.94 [0.46; 1.91]	0.858
Shared medical decision (based on participant opinion)	Missing (*N*=31)				
	Yes indeed (*N*=58) (Reference)	27.6%	0.562		
	A lot – Not at all (*N*=68)	32.4%		1.26 [0.58; 2.71]	0.562
Age of the practitioner	30–49 years old (*N*=90)	34.4%	0.988	1.01 [0.52; 1.96]	0.988
	50 years old or more (*N*=67) (Reference)	34.3%			

Abbreviations: *anti-CCP*, anti-cyclic citrullinated peptide; *b/tsDMARD*, biologic and targeted synthetic disease-modifying antirheumatic drugs; *CI*, confidence interval; *CRP*, c-reactive protein; *CQR19*, Compliance Questionnaire Rheumatology (19-items); *HAQ-DI*, Health Assessment Questionnaire–Disability Index; M24, study visit 24 months after b/tsDMARD initiation; *MTX*, methotrexate; *OR*, odds ratio.

Supplementary Table S4. Factors in favour of same MTX treatment maintenance

Explanatory Factor		M24 visit
Rheumatologist practice: Exclusive hospital-based practice versus Private practice with partial hospital-based practice [a]	OR [95% CI] *p*	2.94 [0.98; 8.85] 0.055
Participant age	OR [95% CI] *p*	1.04 [1.01, 1.08] 0.011
Disease activity evaluated by the participant (visual analogue scale 100–mm)	OR [95% CI] *p*	1.02 [1.00, 1.04] 0.0050
Smoking status: Former smoker, or non-smoker versus Current smoker [a]	OR [95% CI] *p*	1.95 [0.66; 5.78] 0.231

[a] Reference for multivariate analysis.

Note: The following factors were tested in univariate logistic regression and not retained in further analysis: b/tsDMARD monotherapy versus combination therapy; HAQ-DI score; corticosteroids taken at inclusion (yes versus no); treatment observance (CQR19 score); MTX mode of administration before inclusion (self-administered subcutaneous or oral versus injection administered by someone else); obesity (yes versus no); professional activity (yes versus no); comorbidities (yes versus no); rheumatoid factor (positive versus negative); anti-CCP antibodies (positive versus negative); time since diagnosis; presence of radiologic signs (yes versus no); number of swollen joints; CRP levels; shared medical decision-making between participant and practitioner (yes versus no); participation in a global therapeutic program (yes versus no); and the age of the practitioner. The multivariable analysis was adjusted for centre-level clustering effect.

Abbreviations: *anti-CCP*, anti-cyclic citrullinated peptide; *b/tsDMARD*, biologic and targeted synthetic disease-modifying antirheumatic drugs; *CI*, confidence interval; *CRP*, c-reactive protein; *CQR19*, Compliance Questionnaire Rheumatology (19-items); *HAQ-DI*, Health Assessment Questionnaire–Disability Index; M24, study visit 24 months after b/tsDMARD initiation; *MTX*, methotrexate; *OR*, odds ratio.