Online-only supplements

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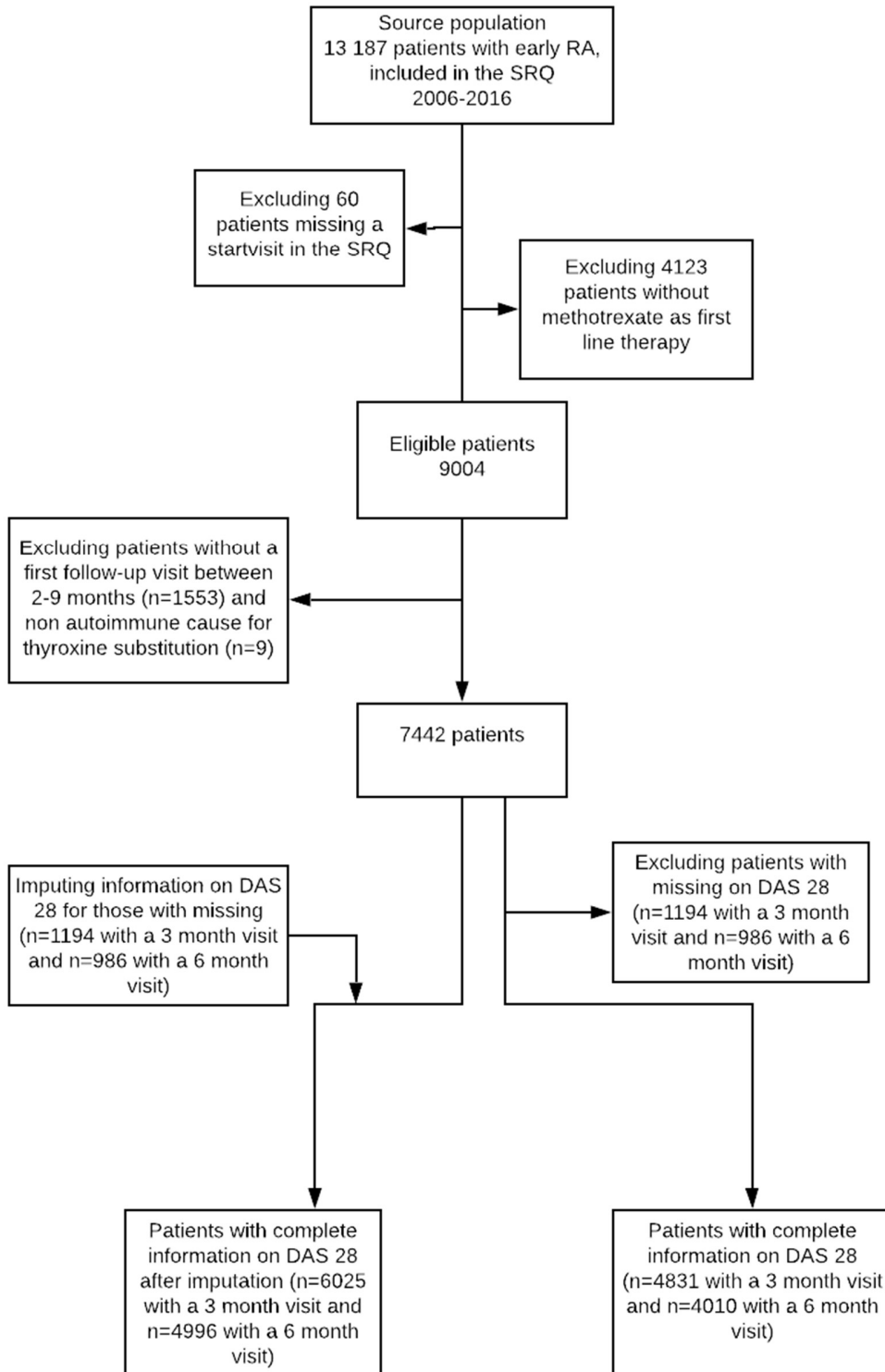
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Figure 1: Flowchart of patients

eText 1

Description of standard treatment guidelines and tight-control follow-up in Swedish Rheumatology Units

Methotrexate is the standard initial treatment for all patients with newly diagnosed RA in Swedish Rheumatology units, as long as there is no contraindication. The dose of Methotrexate is increased up to 20 mg per week, based on the disease activity score (DAS28-ESR). In addition, orally Prednisolone in low-dose the first 12 months, is recommended by the Swedish Society for Rheumatology. According to the Swedish guidelines a patient with early RA should be followed-up with tight control, resulting in a visit to the rheumatologist approximately every third month the first year after diagnosis. The goal is to treat the patient to remission, with a DAS28-ESR less than 2.6.

eText 2

ATC codes in the Swedish prescribed drug register:

H03AA01= levothyroxine, T4 (levaxin+euthyrox), H03AA02= liothyronin, T3 (liothyronin)

Excluding participants with prescriptions for iodine-containing drugs in the Swedish prescribed drug register: ATC-code: C01BD01 (Amiodarone), ATC-code: N05AN01 (Litium), (ATC-code:L03AB01/L03AB04/L03AB05 (Interferon-alfa/alfa 2a/alfa 2b).

ICD-codes in the Swedish cancer register:

Excluding participants with diagnosis codes for thyroid cancer in the Swedish cancer register icd7=194 or icd9=193 or icd10=c73

eText3

Description of missing data of the DAS28 components

The number of missing for the DAS28 variables was approximately 20% overall. For every DAS28 component the number of missing at baseline was: 7% for patient global, 5% for ESR, 2% for swollen joint count, 2% for tender joint count and 12% for DAS28. The corresponding figures for the 3 month visit was: 4% for patient global, 7% for ESR, 1% for Swollen joint count, 2% for Tender joint count and 11% for DAS28.

Description of multiple imputation

Missing values were sequentially imputed using logistic regression models. Variables with missing information that were imputed: smoking, response states (non/moderate and good EULAR response), Health Assessment Questionnaire Disability Index (HAQ), (scoring disability from 0-3, where 0=no disability, 3=unable to to). These variables were imputed using the following variables as predictors: prednisolone, sex, rheumatoid factor,

radiological joint damage, age, AITD, DAS28-ESR, DAS28-CRP, tender joint count, patients' global assessment, ESR, CRP, swollen joint count, VAS pain, physicians´ assessment of disease activity (add scale), sero-status (RF positive/negative), quality of life (EQ5D) and fatigue (100 mm visual analog scale). In the following imputation steps, the variables previously imputed were additionally included as predictors. Fifty imputed datasets were created and analyzed by logistic regression applying the generalized-estimating-equation method when estimating parameters and covariance matrices, which then were analyzed by the procedure MIANALYZE. To compare the imputed datasets, we also performed a complete case analysis.

Appendix Table I. DAS28 parameters at baseline and at the 6-month follow-up visit for RA-patients in the Swedish Rheumatology Quality Register (SRQ), 2006-2016

	Patients with complete information at 6 month follow-up (n=4010)							
	Baseline				6 months follow-up visit			
	AITD+ (n=441)	AITD- (n=3569)	mean difference estimate(ß)	95% CI	AITD+	AITD-	mean difference estimate(ß)	95% CI
Patient global, mean ±SD	54.6 ±27.1	50.7 ±25.8	1.33	0.21 to 5.41	32.7 ±25.5	29.8 ±25.0	2.05	-0.47 to 4.56
ESR, mean ±SD	32.7 ±22.5	31.4 ±23.6	-0.72	-3.03 to 1.60	18.5 ±15.3	16.2 ±14.2	0.86	-0.56 to 2.27
SJC, mean ±SD	7.8 ±5.7	7.7 ±5.6	0.03	-0.53 to 0.59	2.0 ±3.2	1.9 ±3.0	0.05	-0.26 to 0.35
TJC, mean ±SD	7.4 ±5.9	7.3 ±5.9	0.06	-0.54 to 0.66	2.8 ±4.4	2.5 ±3.9	0.28	-0.13 to 0.68
DAS28, mean ±SD	5.1 ±1.4	5.0 ±1.4	0.04	-0.10 to 0.18	3.2 ±1.3	3.0 ±1.3	0.09	-0.05 to 0.22
HAQ, mean ±SD	1.1 ±0.7	1.0 ±0.6	0.08	0.02 to 0.15	0.6 ±0.6	0.5 ±0.5	0.04	-0.01 to 0.10
VAS pain, mean ±SD	55.4 ±27.6	51.7 ±25.6	3.13	0.53 to 5.72	31.4 ±25.7	28.8 ±24.6	2.12	-0.36 to 4.61

Abbreviations: RA=rheumatoid arthritis, AITD= autoimmune thyroid disease, 95% CI=95% confidence interval, ESR=erythrocyte sedimentation rate, SJC=swollen joint count, TJC=tender joint count, HAQ=health assessment questionnaire, SD=Standard deviation. For each of the seven variables named in the first column and for each time point, the estimate (ß) was provided by a linear regression model for which the variable in the first column was the dependent variable, AITD the independent variable, and age and sex used as adjustment. The estimate ß gives the mean difference (given the linear model) between the two types of patients, a positive value meaning that the AITD+ patients have on average a higher value than the AITD- patients.

Appendix Table II. Changes in DAS28 parameters from baseline to 3 and 6 months, among RA-patients in the Swedish Rheumatology Quality Register (SRQ)

	Patients with complete information at 3 months follow-up visit (n=4831)					Patient with complete information at 6 months follow-up visit (n=4010)				
	AITD+ n=531	AITD- n=4301	mean difference estimate (ß)	95% CI	*P*	AITD+ n=441	AITD- n=3569	mean difference estimate (ß)	95% CI	*P*
Δ Patient global, mean±SD	27.6 (29.1)	23.7 (29.2)	0.62	-1.46 to 2.70	0.5607	22.0 (32.6)	20.9 (30.2)	-1.29	-3.71 to 1.13	0.2953
Δ ESR, mean±SD	15.0 (22.1)	15.1 (21.1)	-0.60	-1.81 to 0.62	0.3361	14.2 (19.5)	15.2 (21.7)	-1.04	-2.33 to 0.25	0.1156
Δ SJC, mean±SD	5.6 (5.7)	5.8 (5.5)	-0.07	-0.35 to 0.22	0.6485	5.9 (6.0)	5.9 (5.8)	-0.04	-0.34 to 0.26	0.7733
Δ TJC, mean±SD	4.8 (6.0)	4.8 (5.9)	-0.25	-0.60 to 0.10	0.1585	4.6 (6.1)	4.8 (6.0)	-0.26	-0.65 to 0.12	0.1759
Δ DAS28, mean±SD	2.0 (1.6)	2.0 (1.5)	-0.03	-0.14 to 0.08	0.588	1.9 (1.6)	2.0 (1.6)	-0.08	-0.20 to 0.05	0.2417

Abbreviations: RA=rheumatoid arthritis, AITD= autoimmune thyroid disease, 95% CI=95% confidence interval, ESR=erythrocyte sedimentation rate, SJC=swollen joint count, TJC=tender joint count, HAQ=health assessment questionnaire, SD=Standard deviation. For each of the variables named in the first column and for each time point, the estimate (ß) was provided by a linear regression model for which the variable in the first column was the dependent variable, AITD the independent variable, and age, sex and baseline DAS28/DAS28 parameter used as adjustment. The estimate (ß) shows how differently the two types of patients were evolving between baseline and 3/6 months. For a given variable in the first column, a positive value means that the AITD+ patients have on average evolved (decreased) more than the AITD- patients.

Appendix Table III. DAS28 parameters at baseline, 3 and 6 months for RA-patients <45 years in the SRQ, 2006-2016

mean, ±SD	Patients with complete information at 3 month follow-up visit (n=483)								Patients with complete information at 6 month follow-up visit (n=424)							
	Baseline				3 months follow-up visit				Baseline				6 months follow-up visit			
	AITD+	AITD-	estimate(ß)	(95% CI)	AITD+	AITD-	estimate (ß)	95% CI	AITD+	AITD-	estimate (ß)	95% CI	AITD+	AITD-	estimate (ß)	95% CI
	n=37	n=446			n=37	n=446			n=24	n=400			n=24	n=400		
Patient global	49.3 (21.5)	52.4 (23.9)	-3.54	-11.57 to 4.50	35.1 (22.1)	29.1 (24.8)	5.98	-2.37 to 14.34	47.4 (23.0)	51.1 (24.3)	-3.43	-13.49 to 6.62	37.7 (29.2)	29.2 (25.6)	8.36	-2.36 to 19.08
ESR	23.2 (23.8)	22.1 (19.7)	0.73	-6.04 to 7.50	12.1 (11.3)	11.3 (11.2)	0.47	-3.28 to 4.23	20.9 (20.8)	22.8 (20.7)	-2.20	-10.73 to 6.33	11.1 (11.5)	11.2 (11.5)	-0.39	-5.12 to 4.35
SJC	5.9 (5.5)	6.9 (5.1)	-0.97	-2.71 to 0.78	2.1 (2.8)	2.0 (2.9)	0.07	-0.93 to 1.06	7.0 (5.8)	7.0 (5.2)	0.13	-2.03 to 2.30	2.0 (2.7)	1.6 (2.6)	0.46	-0.64 to 1.55
TJC	6.5 (5.3)	7.7 (6.0)	-1.25	-3.26 to 0.75	2.7 (2.9)	2.8 (4.0)	-0.19	-1.53 to 1.16	7.1 (5.7)	7.9 (6.1)	-0.77	-3.28 to 1.74	3.3 (4.0)	2.6 (4.1)	0.65	-1.04 to 2.34
DAS28	4.5 (1.3)	4.7 (1.4)	-0.26	-0.72 to 0.20	3.0 (1.1)	2.8 (1.4)	0.18	-0.28 to 0.63	4.6 (1.4)	4.7 (1.4)	-0.16	-0.74 to 0.42	3.0 (1.2)	2.7 (1.3)	0.32	-0.22 to 0.87
HAQ	0.9 (0.6)	0.9 (0.6)	-0.03	-0.23 to 0.18	0.4 (0.4)	0.4 (0.5)	-0.04	-0.21 to 0.13	1.0 (0.7)	0.9 (0.6)	0.09	-0.18 to 0.36	0.5 (0.4)	0.4 (0.5)	0.10	-0.11 to 0.31
VAS pain	55.0 (24.8)	54.9 (23.6)	0.45	-7.55 to 8.45	36.9 (23.7)	29.1 (24.4)	8.49	0.24 to 16.73	59.0 (25.1)	54.8 (24.4)	4.76	-5.34 to 14.85	36.1 (25.6)	29.6 (24.8)	6.71	-3.60 to 17.02

Abbreviations: RA=rheumatoid arthritis, AITD= autoimmune thyroid disease, 95% CI=95% confidence interval, ESR=erythrocyte sedimentation rate, SJC=swollen joint count, TJC=tender joint count, HAQ=health assessment questionnaire, SD=Standard deviation. For each of the seven variables named in the first column and for each time point, the estimate (ß) was provided by a linear regression model for which the variable in the first column was the dependent variable, AITD the independent variable, and age and sex used as adjustment. The estimate ß gives the mean difference (given the linear model) between the two types of patients, a positive value meaning that the AITD+ patients have on average a higher value than the AITD- patients.

Appendix Table IV. Changes in DAS28 parameters from baseline to 3 and 6 months, among RA-patients <45 years in the Swedish Rheumatology Quality Register (SRQ)

	Patients with complete information at 3 months follow-up visit (n=483)					Patient with complete information at 6 months follow-up visit (n=424)				
	AITD+	AITD-	mean difference	95% CI	*P*	AITD+	AITD-	mean difference	95% CI	*P*
	n=37	n=446	estimate (ß)3			n=24	n=400	estimate (ß)3		
Δ Patient global, mean±SD	14.2 (24.9)	23.3 (28.9)	-9.52	-19.22 to 0.18	0.05	9.7 (34.6)	21.9 (29.7)	-11.8	-24.26 to 0.70	0.06
Δ ESR, mean±SD	11.1 (20.7)	10.8 (17.5)	0.26	-5.77 to 6.28	0.93	9.8 (16.2)	11.6 (19.1)	-1.81	-9.67 to 6.04	0.65
Δ SJC, mean±SD	3.9 (5.8)	4.9 (5.0)	-1.04	-2.74 to 0.67	0.23	5.1 (5.0)	5.4 (5.2)	-0.32	-2.49 to 1.85	0.77
Δ TJC, mean±SD	3.8 (5.7)	4.9 (5.7)	-1.07	-3.01 to 0.87	0.28	3.8 (5.0)	5.3 (6.3)	-1.43	-4.01 to 1.15	0.28
Δ DAS28, mean±SD	1.4 (1.6)	1.9 (1.5)	-0.44	-0.94 to 0.07	0.09	1.5 (1.6)	2.0 (1.6)	-0.49	-1.15 to 0.18	0.15
Δ HAQ, mean±SD	0.5 (0.6)	0.5 (0.6)	-0.02	-0.23 to 0.18	0.82	0.5 (0.7)	0.5 (0.6)	0	-0.27 to 0.27	0.99
Δ VAS pain, mean±SD	18.1 (27.6)	26.3 (29.4)	-8.20	-17.89 to 1.48	0.10	22.8 (33.2)	25.1 (28.9)	-1.95	-14.06 to 10.15	0.75

Abbreviations: RA=rheumatoid arthritis, AITD= autoimmune thyroid disease, 95% CI=95% confidence interval, ESR=erythrocyte sedimentation rate, SJC=swollen joint count, TJC=tender joint count, HAQ=health assessment questionnaire, SD=Standard deviation. For each of the seven variables named in the first column and for each time point, the estimate (ß) was provided by a linear regression model for which the variable in the first column was the dependent variable, AITD the independent variable, and age and sex used as adjustment. The estimate (ß) shows how differently the two types of patients were evolving between baseline and 3/6 months. For a given variable in the first column, a positive value means that the AITD+ patients have on average evolved (decreased) more than the AITD- patients.

Appendix Table V. Association between autoimmune thyroid disease and response to methotrexate at 3 month follow-up visit among 4831 RA-patients (2666 non/moderate-, 2165 good responders) in the Swedish Rheumatology Quality Register (SRQ), non-imputed dataset

	Number (%) of AITD in non/moderate responders[a] (cases)	Number (%) of AITD in good responders[a] (controls)	OR (95% CI)[b]
Overall	291 (11)	239 (11)	0.92 (0.77-1.11)
Sex			
women	259 (14)	208 (15)	0.89 (0.73-1.09)
men	32 (4)	31 (4)	1.09 (0.65-1.80)
Agegroup			
<45 years	25 (10)	12 (5)	1.88 (0.92-3.87)
>=45 years	266 (11)	227 (12)	0.87 (0.72-1.06)
Serostatus			
RF and/or ACPA positive	198 (11)	158 (11)	0.93 (0.74-1.17)
RF and ACPA negative	80 (10)	69 (11)	0.90 (0.63-1.27)
serostatatus unspecified	13 (21)	12 (18)	1.09 (0.44-2.68)

Abbreviations: RA=rheumatoid arthritis, AITD= autoimmune thyroid disease, OR=odds ratio, 95% CI=95% confidence interval, a According to EULAR response criteria. If change of dmard at follow-up visit=non responder. Values are the numbers (%). b Adjusted for age and sex

Appendix Table VI. Association between autoimmune thyroid disease and response to methotrexate at 6 month follow-up visit among 4996 RA-patients (3019 non/moderate-, 1977 good responders) in the Swedish Rheumatology Quality Register (SRQ), imputed dataset.

	Number (%) of AITD in non/moderate responders[a] (cases)	Number (%) of AITD in good responders[a] (controls)	OR (95% CI)[b]	OR (95% CI)[c]
Overall	360 (12)	199 (10)	1.16 (0.95-1.42)	1.14 (0.93-1.40)
Sex				
women	323 (15)	176 (14)	1.25 (0.91-1.39)	1.10 (0.88-1.36)
men	37 (4)	23 (3)	1.38 (0.77-2.47)	1.37 (0.76-2.46)
Agegroup				
<45 years	28 (8)	6 (3)	2.75 (1.04-7.28)	2.69 (1.00-7.23)
>=45 years	332 (12)	193 (11)	1.11 (0.90-1.37)	1.09 (0.89-1.35)
Serostatus				
RF and/or ACPA positive	254 (12)	131 (10)	1.24 (0.97-1.58)	1.21 (0.95-1.55)
RF and ACPA negative	96 (11)	58 (10)	1.11 (0.76-1.61)	1.10 (0.75-1.60)
serostatatus unspecified	10 (13)	10 (23)	0.47 (0.16-1.42)	0.44 (0.14-1.41)

[a] According to EULAR response criteria including imputet values on response status. Values are the numbers (%). Abbreviations: RA=rheumatoid arthritis, AITD= autoimmune thyroid disease, OR=odds ratio, 95% CI=95% confidence interval, [b] Adjusted for age and sex, [c] Adjusted for age, sex, haq, smoking, cortisone. Multiple imputations=50.

Appendix Table VII. Association between autoimmune thyroid disease and response to methotrexate at 6 month follow-up visit among 4010 RA-patients (2352 non/moderate-, 1658 good responders) in the Swedish Rheumatology Quality Register (SRQ), non-imputed dataset

	Number of AITD in non/moderate responders[a] (cases)	Number of AITD in good responders[a] (controls)	OR (95% CI)[b]
Overall	282 (12)	159 (10)	1.22 (0.99-1.50)
Sex			
women	252 (15)	142 (14)	1.15 (0.92-1.44)
men	30 (4)	17 (3)	1.70 (0.93-3.12)
Agegroup			
<45 years	20 (8)	4 (2)	3.39 (1.13-10.16)
>=45 years	262 (13)	155 (10)	1.16 (0.93-1.43)
Serostatus			
RF and/or ACPA positive	190 (12)	105 (10)	1.23 (0.95-1.58)
RF and ACPA negative	84 (12)	45 (9)	1.35 (0.91-2.01)
serostatatus unspecified	8 (15)	9 (24)	0.55 (0.18-1.73)

[a] According to EULAR response criteria. If change of dmard at follow-up visit=non responder. Values are the numbers (%). Abbrevations: RA=rheumatoid arthritis, AITD= autoimmune thyroid disease, OR=odds ratio, 95% CI=95% confidence interval, [b] Adjusted for age and sex