

Supplement

Supplementary Table 1

Medication	Corresponding Anatomical Therapeutic Chemical (ATC) - code
bDMARDs Etanercept Adalimumab Tocilizumab other biologics Abatacept Anakinra Canakinumab Certolizumab Golimumab Infliximab Rituximab Secukinumab Sarilumab	L04AB01 L04AB04 L04AC07 L04AA24 L04AC03 L04AC08 L04AB05 L04AB06 L04AB02 L01XC02 L04AC10 L04AC14
sDMARDs Methotrexate other cDMARDs Azathioprine Baricitinib Cyclophosphamide Chloroquine Hydroxychloroquine Leflunomide Mycophenolate Penicillamine Sulfasalazine Tofacitinib	L01BA01, L04AX03, M01CX01 L04AX01 L04AA37 L01AA01 P01BA01 P01BA02 L04AA13 L04AA06 M01CC01 M01CX02 L04AA29
NSAIDs	M01 (antiinflammatory and antirheumatic products)
Systemic glucocorticoids	H02 (corticosteroids for systemic use)
Antihypertensive drugs	C02 (antihypertensives), C07 (beta blocking agents), C08 (calcium channel blockers), C09 (agents acting on the renin-angiotensin system)
Antithrombotic agents	B01 (antithrombotic agents)
Lipid modifying agents	C10 (lipid modifying agents)
Drugs used in diabetes	A10 (drugs used in diabetes)
Analgesics Opioid drugs other analgetics and antipyretics (NSAIDs excluded)	N02A (opioids) N02B (other analgesics and antipyretics)
Antiepileptic drugs	N03 (antiepileptics)
Psycholeptic drugs Antipsychotic drugs Anxiolytic drugs	N05 (psycholeptics) N05A (antipsychotics) N05B (anxiolytics)

Antidepressant drugs	N06A (antidepressants)
Eye anti-infectives and anti-inflammatory agents	S01A (antiinfectives), S01B (anti-inflammatory agents), S01C (anti-inflammatory agents and antiinfectives in combination)
Antiglaucoma preparations and miotics	S01E (antiglaucoma preparations and miotics)
Antiinfectives for systemic use	J (antiinfectives for systemic use)
Drugs affecting bone structure and mineralization	M05B (drugs affecting bone structure and mineralization)
Drugs for acid related disorders	A02 (drugs for acid related disorders)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	A07 (antidiarrheals, intestinal antiinflammatory/antiinfective agents)
Thyroid therapy	H03 (thyroid therapy)

Supplementary Table 2: Physician's global assessment of disease activity and patient-reported outcomes (all assessed using NRS 0-10) for males and females by JIA category

	Male	Female	p value [¶]
sJIA (m 34 / f 32)			
Physician's global assessment of disease activity	1.2 (1.5)	2.4 (2.4)	0.072
Patient-reported disease activity	1.8 (1.8)	2.9 (2.2)	0.027
Patient-reported pain	1.7 (2.0)	2.8 (2.5)	0.052
Patient-reported fatigue	2.4 (2.0)	3.2 (2.8)	0.172
PersOA (n 44 / f 73)			
Physician's global assessment of disease activity	1.3 (1.6)	1.9 (1.9)	0.291
Patient-reported disease activity	1.7 (2.1)	2.6 (2.2)	0.031
Patient-reported pain	1.1 (1.7)	2.5 (2.5)	<0.001
Patient-reported fatigue	1.3 (2.0)	2.8 (2.5)	<0.001
ExtOA (m 48 / f 179)			
Physician's global assessment of disease activity	0.8 (0.8)	2.0 (2.1)	0.001
Patient-reported disease activity	2.6 (2.1)	3.1 (2.2)	0.145
Patient-reported pain	2.1 (2.2)	3.0 (2.4)	0.026
Patient-reported fatigue	2.7 (2.6)	3.5 (2.8)	0.069
RF- PA (m 68 / f 282)			
Physician's global assessment of disease activity	1.1 (1.8)	1.9 (2.2)	0.072
Patient-reported disease activity	2.4 (2.4)	3.1 (2.2)	0.021
Patient-reported pain	2.2 (2.4)	3.0 (2.4)	0.016
Patient-reported fatigue	2.7 (2.5)	3.7 (2.8)	<0.001
RF+ PA (m 16 / f 99)			
Physician's global assessment of disease activity	1.3 (2.1)	2.1 (2.2)	0.317
Patient-reported disease activity	2.6 (2.4)	3.0 (2.2)	0.539
Patient-reported pain	2.4 (2.5)	2.8 (2.3)	0.485
Patient-reported fatigue	3.5 (3.4)	3.5 (2.7)	0.995
ErA (m 155 / f 113)			
Physician's global assessment of disease activity	1.6 (2.0)	1.4 (1.7)	0.603
Patient-reported disease activity	2.1 (2.0)	2.9 (2.4)	0.007
Patient-reported pain	1.8 (2.1)	2.9 (2.6)	<0.001
Patient-reported fatigue	2.1 (2.4)	3.4 (3.0)	<0.001
PsA (m 41 / f 75)			
Physician's global assessment of disease activity	1.9 (1.8)	2.1 (2.5)	0.818
Patient-reported disease activity	2.8 (2.6)	3.6 (2.5)	0.099
Patient-reported pain	2.8 (2.7)	3.2 (2.3)	0.376
Patient-reported fatigue	3.1 (2.8)	4.1 (2.7)	0.058
undiffA (m 14 / f 33)			
Physician's global assessment of disease activity	0.9 (0.6)	2.3 (2.3)	0.133
Patient-reported disease activity	2.3 (2.6)	3.0 (2.7)	0.431
Patient-reported pain	1.7 (2.3)	3.1 (2.9)	0.127
Patient-reported fatigue	1.3 (2.0)	4.1 (2.7)	0.001

Values are mean (standard deviation)

sJIA – Systemic JIA, PersOA – Persistent oligoarthritis, ExtOA – Extended oligoarthritis, RF- PA – Rheumatoid factor-negative polyarthritis, RF+ PA – RF-positive polyarthritis, ErA – Enthesitis-related arthritis, PsA – Psoriatic arthritis, undiffA – Undifferentiated arthritis

[¶] p value from Welch-Test

Supplementary Table 3: Outcome parameters related to the continuously distributed number of non-DMARD medication

Parameters	OR [¶]	95% CI	P- Value
Age, ys,	1.05	1.03 ; 1.07	<0.001
Female, N (%)	2.34	1.89 ; 2.91	<0.001
Disease duration, ys	1.05	1.03 ; 1.06	<0.001
Patient-reported disease activity, (NRS 0-10)	1.36	1.30 ; 1.42	<0.001
Patient-reported pain, (NRS 0-10)	1.32	1.27 ; 1.38	<0.001
Patient-reported fatigue, (NRS 0-10)	1.22	1.18 ; 1.27	<0.001
HAQ total score (range 0-3)	3.80	3.11 ; 4.63	<0.001
Patient-reported HRQoL, SF-36, mental component summary score	0.98	0.97 ; 0.99	<0.001
Patient-reported HRQoL, SF-36, physical component summary score	0.93	0.92 ; 0.93	<0.001
Time from symptom onset to 1 st bDMARD in years	1.06	1.03 ; 1.08	<0.001

NRS – numerical rating scale, HAQ –Health Assessment Questionnaire, HRQoL – Health-related quality of life, SF-36 – Short Form-36, OR – odds ratio, 95% CI – 95% confidence interval

¶ OR from ordinal logistic regression in order to analyse the association between number of non-DMARDs and each parameter separately

Supplementary Table 4: Medication use in general and use of selected medications by time from onset of symptoms to bDMARD start for the entire study group and for patients with systemic JIA and polyarticular-onset JIA.

JIA category	G1 ≤2 years			G2 >2 to <5 years					G3 ≥ 5 years				
	all	Sys JIA	RF-/RF+ PA	all	OR (95% CI)	P- Value	Sys JIA	RF-/RF+ PA	all	OR (95% CI)	P- Value	Sys JIA	RF-/RF+ PA
n	267	20	123	334			17	135	448			25	132
Number of medicines per patient (incl. DMARD), mean (SD)	2.2 (2.0)	1.4 (1.6)	2.4 (2.0)	2.5 (2.0)	0.26 (-0.07, 0.59)	0.124	3.2 (2.5)	2.5 (2.0)	2.9 (2.2)	0.49 (0.14, 0.83)	0.005	3.8 (2.6)	3.1 (2.2)
Age, ys, Mean (SD)	22.1 (3.4)	21.5 (3.1)	22.0 (3.2)	23.1 (4.2)	0.44 (-0.27, 1.15)	0.224	22.2 (4.8)	23.5 (4.2)	24.2 (4.7)	1.30 (0.62, 1.99)	<0.001	27.2 (4.8)	25.2 (5.1)
Female gender	162 (60.7)	9 (45.0)	99 (80.5)	219 (65.6)	1.12 (0.78, 1.61)	0.527	7 (41.2)	106(78.5)	330 (73.7)	1.42 (0.99, 2.03)	0.053	13 (52.0)	112 (84.8)
Disease duration, ys, Mean (SD)	9.1 (4.0)	11,0 (4.8)	9.1 (3.6)	12.1 (4.5)	2.72 (1.99, 3.45)	<0.001	15.3 (4.1)	12.4 (4.5)	18.5 (5.5)	8.98 (8.24, 9.73)	<0.001	22.8 (4.5)	19.4 (5.6)
Medication													
DMARDs	170 (63.7)	9 (45.0)	87 (70.7)	237 (71.0)	1.63 (1.13, 2.34)	0.009	15 (88.2)	92 (68.2)	356 (79.5)	2.31 (1.61, 3.34)	<0.001	20 (80.0)	107 (81.1)
NSAIDs	109 (40.8)	0	58 (47.2)	164 (49.1)	1.39 (0.99, 1.97)	0.060	8 (47.1)	67 (49.6)	224 (50.0)	1.20 (0.85, 1.68)	0.303	11 (44.0)	63 (47.7)
Systemic glucocorticoids	41 (15.4)	4 (20.0)	28 (22.8)	60 (18.0)	1.14 (0.69, 1.88)	0.604	6 (35.3)	28 (20.7)	127 (28.3)	1.67 (1.06, 2.63)	0.028	15 (60.0)	46 (34.8)
Analgesics	26 (9.7)	0	15 (12.2)	32 (9.6)	0.99 (0.53, 1.87)	0.982	1 (5.9)	16 (11.9)	60 (13.4)	1.17 (0.65, 2.13)	0.596	7 (28.0)	24 (18.2)
Opioid drugs	3 (1.1)	0	1 (0.8)	18 (5.4)	2.83	0.144	1 (5.9)	6 (4.4)	22 (4.9)	2.57	0.162	5 (20.0)	6 (4.5)

					(0.70, 11.41)					(0.68, 9.63)			
Antiinfectives for systemic use	16 (6.0)	2 (10.0)	6 (4.9)	17 (5.1)	0.95 (0.45, 1.97)	0.880	1 (5.9)	6 (4.4)	31 (6.9)	0.96 (0.50, 1.85)	0.906	3 (12.0)	7 (5.3)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	13 (4.9)	1 (5.0)	5 (4.1)	12 (3.6)	0.67 (0.29, 1.57)	0.360	1 (5.9)	4 (3.0)	21 (4.7)	0.89 (0.42, 1.91)	0.766	0	3 (2.3)
Antidepressant drugs	3 (1.1)	0	1 (0.8)	11 (3.3)	3.11 (0.83, 11.61)	0.091	0	4 (3.0)	25 (5.6)	4.29 (1.23, 14.98)	0.022	4 (16.0)	4 (3.0)
Antihypertensive drugs	5 (1.9)	0	4 (3.3)	10 (3.0)	1.38 (0.44, 4.37)	0.581	1 (5.9)	4 (3.0)	21 (4.7)	1.92 (0.63, 5.79)	0.249	6 (24.0)	8 (6.1)
Eye antiinfectives and antiinflammatory agents	4 (1.5)	0	0	6 (1.8)	0.91 (0.25, 3.37)	0.891	0	0	11 (2.5)	1.50 (0.47, 4.75)	0.492	0	4 (3.0)
Psycholeptic drugs (incl. antipsychotic & anxiolytic drugs)	2 (0.7)	0	1 (0.8)	3 (0.9)	1.44 (0.23, 9.05)	0.696	1 (5.9)	1 (0.7)	11 (2.5)	2.63 (0.51, 13.48)	0.245	0	1 (0.8)
Antithrombotic agents	3 (1.1)	0	3 (2.4)	2 (0.6)	0.97 (0.15, 6.09)	0.972	0	1 (0.7)	9 (2.0)	3.34 (0.84, 13.42)	0.088	3 (12.0)	3 (2.3)

The values are N (%) unless indicated otherwise.

OR – odds ratio, 95% CI – 95% confidence interval, sys JIA – systemic JIA, RF-/RF+ PA – rheumatoid factor positive and RF negative polyarthritis

Linear (continuously distributed parameters) and logistic regression (categorical parameters) models were applied to analyse the continuous time from symptom onset to bDMARD start and to compare medication use at follow-up between the three groups, G1, G2 and G3, adjusting for the generalised propensity score and disease activity at last follow-up

Supplementary Table 5: Medication use in general and use of selected medications by time of JIA disease onset

	Disease onset before the year 2000	Disease onset after the year 2000	OR [¶]	95% CI	p value
DMARDs	257 (72.0)	565 (60.5)	0.44	0.33 ; 0.60	<0.001
sDMARDs	103 (28.9)	263 (28.2)	0.74	0.54 ; 1.00	0.047
bDMARDs	225 (63.0)	467 (50.0)	0.49	0.37 ; 0.66	<0.001
NSAIDs	184 (51.5)	430 (46.0)	0.67	0.51 ; 0.88	0.004
Systemic glucocorticoids	111 (31.1)	134 (14.4)	0.46	0.33 ; 0.65	<0.001
Analgesics	46 (12.9)	72 (7.7)	0.77	0.49 ; 1.21	0.254
Opioid drugs	21 (5.9)	21 (2.3)	0.48	0.24 ; 0.98	0.043
Antiinfectives for systemic use	21 (5.9)	59 (6.3)	0.99	0.56 ; 1.75	0.959
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	13 (3.6)	49 (5.3)	1.32	0.66 ; 2.63	0.433
Antidepressant drugs	19 (5.3)	25 (2.7)	0.48	0.24 ; 0.95	0.036
Antihypertensive drugs	28 (7.8)	13 (1.4)	0.28	0.13 ; 0.60	0.001
Eye antiinfectives and anti- inflammatory agents	8 (2.2)	15 (1.6)	0.68	0.26 ; 1.81	0.438
Psycholeptic drugs (incl. anti- psychotic and anxiolytic drugs)	6 (1.7)	13 (1.4)	0.50	0.17 ; 1.47	0.208
Antithrombotic agents	8 (2.2)	7 (0.8)	0.48	0.15 ; 1.56	0.220

The values are N (%)

OR – odds ratio, 95% CI – 95% confidence interval

Logistic regression analysis was performed to determine the association of medication use at last visit and JIA disease onset before and after the year 2000 adjusted for age and sex at last follow-up. OR for reference disease onset before the year 2000.

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