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ORIGINAL RESEARCH

Medication burden in young adults with juvenile idiopathic arthritis: data from a multicentre observational study

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ABSTRACT

Objective To assess the medication and disease burden of young adults with juvenile idiopathic arthritis (JIA).

Methods Young adults with JIA prospectively followed in the Juvenile Arthritis Methotrexate/Biologics long-term Observation reported on their health status and medication use. All medications taken (disease-modifying antirheumatic drugs (DMARDs)/prescription/over-the-counter drugs, but excluding most local therapies) classified according to the Anatomical Therapeutic Chemical Classification System were included in this analysis. Medication use at last follow-up was evaluated by sex, JIA category and time from symptom onset to the first biological DMARD (bDMARD) start.

Results A total of 1306 young adults (68% female) with JIA and a mean disease duration of 13.6±6 years were included in the study. Patients reported using on average 2.4±2.1 medicines and 1.5±1.7 non-DMARD medicines, respectively, at the last follow-up. Almost a quarter of the patients reported polypharmacy. The higher the number of medications used was, the higher the disease activity, pain and fatigue, and the lower the quality of life of patients. Medication usage differed significantly between sexes and JIA categories, being highest in patients with rheumatoid factor-positive polyarthritis and systemic JIA. The number of medications used was significantly associated with the time from symptom onset to bDMARD start. Patients taking opioids or antidepressants had a particularly high disease burden and had received bDMARDs an average of 2 years later than patients not taking these medications.

Conclusion Medication use in adults with JIA varies depending on sex, JIA category, and the time between symptom onset and initiation of treatment with bDMARD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is well recognised that biological disease-modifying antirheumatic drugs (bDMARDs) are effective in controlling disease activity and reducing long-term consequences of juvenile idiopathic arthritis (JIA).

⇒ However, little is known to date about medication use and comorbidities in adults with JIA.

WHAT THIS STUDY ADDS

⇒ This study characterises medication and disease burden in young people with JIA, with one in four reporting polypharmacy.

⇒ It was found that JIA patients with a late start of bDMARDs were significantly more likely to use DMARDs, glucocorticoids and antidepressants in adulthood in comparison to those with an early bDMARD start.

⇒ Patients with rheumatoid factor-positive polyarthritis and systemic JIA had the highest medication burden among the JIA categories, including the highest rates of glucocorticoid use as well as antihypertensive and antithrombotic use.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The data highlight the need for early effective treatment in JIA, as it can reduce the need for multiple medications in adulthood and prevent treatment-related comorbidities such as hypertension.

⇒ Results suggest that the medication use reported by patients provides important information about the outcome of JIA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) comprises a heterogeneous group of immune-mediated diseases characterised by arthritis of unknown origin with a duration of at least 6 weeks and onset before the age of 16 years.[1] JIA is the most common chronic inflammatory rheumatic disease in childhood and adolescence. Disease course and outcome vary widely between the different JIA categories. However, all JIA patients are at risk for disease- and/or medication-related morbidity, physical disability and/or lifelong quality of life impairment, with at least half requiring drug treatment into adulthood.[2–6] Comorbidities observed in patients with JIA include uveitis, inflammatory bowel disease, osteopenia/-porosis, short stature, anxiety and depression, other autoimmune diseases (eg, thyroiditis)

and cardiovascular risk factors (eg, hypertension, dyslipidaemia, obesity).[7–13] Comorbidities may increase with age and disease duration. They may require additional medications or impact treatment choices and contribute to the disease burden of JIA.[14]

However, information on the burden of comorbidities and their treatments in adults with JIA is still very limited.[15] In JIA registries and long-term outcome studies, the focus is often only on antirheumatic drugs, and therapies for concomitant diseases are not recorded. In addition, rheumatologists are not always aware of patients' concomitant diseases.

To gain more insight into the disease and treatment burden of patients, self-reported data can be used. According to a study by Solomon *et al*, self-reported drug utilisation is valid.[16] The authors emphasised that self-reported medication use can provide new and important information about the impact of a rheumatic disease.

The aim of this study was to assess the medication use of young people with JIA using self-reports. In addition, the rate of polypharmacy and factors associated with multiple medication use in adults with JIA should be identified.

PATIENTS AND METHODS

The analysis was based on data from BiKeR (Biologika in der Kinderrheumatologie (biologics in paediatric rheumatology)) and JuMBO (Juvenile Arthritis Methotrexate/Biologics long-term Observation), the follow-up registry of BiKeR. BiKeR and JuMBO are ongoing multicentre, prospective, observational cohort studies. Both are used to assess the long-term effectiveness and safety of synthetic and biological disease-modifying antirheumatic drugs (s and bDMARDs) in patients with JIA in Germany.[17 18] Patients with JIA according to the International League of Associations for Rheumatology criteria[1] were enrolled in BiKeR at the start of methotrexate (MTX) or biological therapy and continuously followed. On reaching 18 years of age, they were transferred to the JuMBO registry. Written informed consent for participation in BiKeR was obtained from parents and patients (≥8 years) and again from patients (≥18 years) when included in JuMBO.

In both registries, patients were assessed every 6 months using standardised questionnaires. In addition, physicians recorded details of the patients' disease status and antirheumatic medications, including DMARDs with dose and administration method, changes and discontinuations with start and end dates, and reasons for discontinuation.

For this study, all patients with at least one JuMBO visit since the start of the registry until 17 June 2019, were included. The physician's global assessment of disease activity using a Numerical Rating Scale (NRS, range 0–10) was considered for patients with a time corresponding physician visit. Physician-reported data on JIA category, date of disease onset, ANA-positivity and HLA-B27-positivity, and DMARD treatment in childhood and adolescence were extracted from BiKeR.

Outcome parameters and medication assessment

The following patient-reported outcome parameters were evaluated according to the last available follow-up in JuMBO: self-reported disease activity, pain and fatigue, each assessed on a NRS. The patients' functional status was assessed using the Health Assessment Questionnaire.[19] The patients' health-related quality of life (HRQoL) was assessed via the Medical Outcomes Study Short Form 36 (SF-36).[20] The SF-36 survey yields two comprehensive HRQoL indices, the physical component summary and the mental component summary scores. Both summary scores were obtained from normalised and Z-transformed domain scores.

In addition, at each visit, patients indicated what medications they had taken in the past 6 months for rheumatic disease or other reasons. All medication use (DMARDs, prescription and over-the-counter drugs) reported at the last follow-up was used to describe the medication burden. Polypharmacy was defined as the intake of three or more medications regardless of current DMARD therapy. This definition was adapted from the WHO definition of polypharmacy as the simultaneous use of four or more medications.[21] The medications reported by the patients were coded according to the Anatomical Therapeutic Chemical (ATC) classification system.[22] If no drug-specific coding was possible due to inaccurate information, the next suitable top category was assigned, for example, patient-reported medication for hypertension was coded with C02 (antihypertensives). Contraceptives, cough and cold remedies and local therapies were excluded from the evaluation, except for local eye medicines. Certain ATC categories were assigned to disease-specific drug groups, for example, categories C02, C07, C08 and C09 were allocated to the antihypertensive group. Categories S01A-C were assigned to the eye anti-infective and anti-inflammatory agent groups. All drug groups with the corresponding ATC categories can be found in online supplemental table 1.

Statistical analysis

The mean number of medications per patient was compared using univariate analysis of variance between men and women and between JIA categories. χ^2 tests were applied to compare self-reported medication use among male and female patients and among patients with different JIA categories (tables 2 and 3, online supplemental table 2). The kappa statistics were calculated to measure the agreement between physician and patient reports of DMARD use.

A multivariable logistic regression was performed to analyse the association between antihypertensive therapy

and the duration of exposure to systemic glucocorticoids, disease duration and JIA category.

Patient outcome with respect to the number of non-DMARD medications

The number of medications taken regardless of DMARDs was categorised into three groups: group 1: no non-DMARDs, group 2: less than three non-DMARDs and group 3: three or more non-DMARDs. The clinical characteristics at the last follow-up and the concomitant use of selected therapies were compared by multinomial logistic regression analyses between the three groups. Group 2 was the reference group in the analyses (table 4). In addition, the continuous number of non-DMARDs was analysed by ordinal logistic regression analysis (online supplemental table 3).

Medication use by the time from symptom onset to first bDMARD start

The association of time between JIA onset and the start of the first bDMARD and the number of concomitant therapies were visualised by kernel-weighted local polynomial smoothing. The duration between JIA onset and the start of the first bDMARD treatment was categorised into three groups (group A, ≤2 years (early); group B, >2 to ≤5 years (medium) and group C, >5 years (late)). A generalised propensity score was estimated to balance the patients' characteristics between the three groups.[23 24] The propensity score was based on the covariates JIA category, functional status, and disease activity at registry inclusion, year of study inclusion, age at last available documentation and length of follow-up. For more details, please refer to the publication of Minden *et al*.[25] Linear regression analyses for continuously distributed response variables (eg, age) and logistic regression analyses for categorical response variables (eg, use of DMARDs) were applied to estimate the association with the explanatory variables duration between JIA onset and the start of the first bDMARD treatment (eg, G1, G2 and G3), disease activity at the last follow-up and the generalised propensity score (online supplemental table 4). In addition, the association between the year of onset of JIA (before and from the year 2000 (biological era)) with medication use was determined by logistic regression analysis adjusted for age and sex at last follow-up (online supplemental table 5).

The level of significance was 5%, and analyses were performed using SAS software, V.9.4.

Table 1 Patient characteristics at last follow-up

Parameters		Missings
n	1306	
Age, years, mean (SD)	23.1 (4.1)	0
Female, N (%)	886 (67.8)	0
JIA category, N (%)		0
Systemic JIA	66 (5.1)	
Persistent oligoarthritis	117 (9.0)	
Extended oligoarthritis	227 (17.4)	
RF-negative polyarthritis	350 (26.8)	
RF-positive polyarthritis	115 (8.8)	
Enthesitis-related arthritis	268 (20.5)	
Psoriatic arthritis	116 (8.9)	
Undifferentiated arthritis	47 (3.6)	
ANA positive (at BiKeR enrollment), N (%)	536 (41.0)	18 (1.4)
HLA-B27 positive, N (%)	326 (25.0)	18 (1.4)
Disease duration, years, mean (SD)	13.6 (6)	8 (0.6)
Physician's global assessment of disease activity (NRS 0–10), mean (SD), n=621	1.8 (2.0)	685 (52.5)
Patients in clinically inactive disease*, n (%), n=621	252 (40.6)	685 (52.5)
Patient-reported disease activity (NRS 0–10), mean (SD)	2.8 (2.3)	1 (0.1)
Patient-reported pain (NRS 0–10), mean (SD)	2.6 (2.4)	2 (0.2)
Patient-reported fatigue (NRS 0–10), mean (SD)	3.2 (2.8)	1 (0.1)
HAQ total score (range 0–3), mean (SD)	0.29 (0.52)	14 (1.1)
Patient-reported HRQoL, SF-36, mental component summary score, mean (SD)	49.3 (9.6)	44 (3.4)
Patient-reported HRQoL, SF-36, physical component summary score, mean (SD)	46.8 (10.8)	44 (3.4)

*Defined according to Wallace *et al*.[45]
ANA, antinuclear antibodies; bDMARD, biological disease modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; HRQoL, health-related quality of life; JIA, juvenile idiopathic arthritis; NRS, Numerical Rating Scale; RF, rheumatoid factor; SF-36, Short Form-36; ys, years.

RESULTS

Patient characteristics and self-reported medication use

A total of 1306 JIA patients were included. The clinical and sociodemographic characteristics of the cohort at the last follow-up in JuMBO are shown in table 1. Patients had a mean age of 23 years at follow-up. Approximately 79% of them were ever treated with bDMARDs, and the first bDMARD was prescribed 5.4±4.3 years after disease onset on average. Medication use (ie, most used medications and selected medications that may indicate comorbidities) at the last visit is shown in table 2 for the entire study group and by sex. Table 3 shows medication use by JIA category.

At the last follow-up, the average number of medications used was 2.4, and the maximum number was 12 drugs. Approximately two in three patients reported DMARD intake at their last visit, and 208 (15.9%) reported only

Table 2 Medication use in the total study cohort and by sex reported at the last follow-up

Medication	All	Male	Female	P value*
n	1306	420	886	
No of medicines per patient, mean (SD) (incl. DMARD)	2.4 (2.1)	1.9 (1.9)	2.7 (2.2)	<0.001
Current treatment with				
DMARDs	836 (64.0)	256 (61.0)	580 (65.5)	0.113
bDMARDs	700 (53.6)	220 (52.4)	480 (54.2)	0.543
sDMARDs	377 (28.9)	88 (21.0)	289 (32.6)	<0.001
NSAIDs	624 (47.8)	159 (37.9)	465 (52.5)	<0.001
Systemic glucocorticoids	250 (19.1)	42 (10.0)	208 (23.5)	<0.001
Analgesics	139 (10.6)	31 (7.4)	108 (12.2)	0.008
Opioid drugs	44 (3.4)	12 (2.9)	32 (3.6)	0.48
Drugs for acid related disorders	90 (6.9)	26 (6.2)	64 (7.2)	0.491
Antiinfectives for systemic use	80 (6.1)	26 (6.2)	54 (6.1)	0.946
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	64 (4.9)	23 (5.5)	41 (4.6)	0.507
Thyroid therapy	64 (4.9)	9 (2.1)	55 (6.2)	0.001
Antidepressant drugs	45 (3.4)	9 (2.1)	36 (4.1)	0.076
Antihypertensive drugs	41 (3.1)	15 (3.6)	26 (2.9)	0.538
Eye antiinflammatory/antiinfective agents	23 (1.8)	8 (1.9)	15 (1.7)	0.786
Antiepileptic drugs	20 (1.5)	7 (1.7)	13 (1.5)	0.784
Psycholeptic drugs	19 (1.5)	7 (1.7)	12 (1.4)	0.660
Antithrombotic agents	15 (1.1)	1 (0.2)	14 (1.6)	0.034
Drugs used in diabetes	14 (1.1)	4 (1.0)	10 (1.1)	0.773
Antiglaucoma preparations and miotics	8 (0.6)	0	8 (0.9)	–
Drugs affecting bone structure and mineralisation	2 (0.2)	0	2 (0.2)	–
Lipid-modifying agents	2 (0.2)	2 (0.5)	0	–

The values are N (%) unless indicated otherwise.
*Univariable Analysis of variance for continuously distributed parameters or χ^2 test for categorical parameters.
bDMARD, biological DMARD; DMARD, disease modifying antirheumatic drug; NSAIDs, non-steroidal antiinflammatory drugs; sDMARD, synthetic DMARD.

DMARD use. Almost a quarter (23%) of patients were taking at least three non-DMARD medications and exhibited polypharmacotherapy. Approximately one in five patients (235, 18.0%) reported no medication use at all.

The most frequently used DMARD was etanercept in 23.4%, followed by MTX in 22.9%, adalimumab in 13.9% and tocilizumab in 6.8% of patients. Eighteen per cent of patients received s/bDMARD combination therapies. The agreement between reported DMARD use by patients and physicians was substantial (absolute agreement in 88%, n=561 of 635 with matched patient and physician reports about DMARD use, kappa=0.65).

Women took significantly more drugs than men, namely sDMARDs, non-steroidal antiinflammatory drugs (NSAIDs), glucocorticoids, analgesics, thyroid medication, and antithrombotic agents. Women predominated in the JIA categories where the use of sDMARDs, NSAIDS and glucocorticoids was relatively high (table 3). In addition, they tended to have higher disease activity and subjective burden of disease in all JIA categories compared with men (online supplemental table 2).

The intake of NSAIDs and systemic glucocorticoids differed significantly between the JIA categories (p=0.008 and <0.001, respectively). Patients with systemic JIA (sJIA) and rheumatoid factor positive (RF+) polyarthritis were those who used glucocorticoids most frequently (32% and 35%, respectively). These patients also had the highest intake of antihypertensive (11% and 5%, respectively) and antithrombotic drugs (4.5% and 3.5%, respectively). Approximately half of the patients who took antihypertensives were concomitantly treated with systemic glucocorticoids (n=19, 46.3%). Analyses showed a significant association between antihypertensive therapy and duration of exposure to systemic glucocorticoids (p=0.017) and disease duration (p<0.001), controlled for JIA category.

Patient outcome with respect to the number of non-DMARD medications

Table 4 shows the patient characteristics and outcomes for the three groups with different non-DMARD use (none, 1–2, and≥3 non-DMARD medicines). In the

Table 3 Medication use by JIA category reported at the last follow-up

Medication	sJIA	PersOA	ExtOA	RF- PA	RF+PA	ErA	PsA	undiffA	P value*
n	66	117	227	350	115	268	116	47	
Females, %	48.5	62.4	78.9	80.6	86.1	42.2	64.7	70.2	
No of medicines per patient, mean (SD) (incl. DMARD)	2.7 (2.5)	1.7 (1.9)	2.7 (2.2)	2.4 (2.0)	3.3 (2.3)	2.1 (1.8)	2.5 (2.0)	2.3 (2.1)	<0.001
Current treatment with DMARDs	45 (68.2)	53 (45.3)	168 (74.0)	210 (60.0)	100 (87.0)	161 (60.1)	72 (62.1)	27 (57.4)	<0.001
bDMARDs	39 (59.1)	37 (31.6)	145 (63.9)	169 (48.3)	84 (73.0)	143 (53.4)	61 (52.6)	22 (46.8)	<0.001
sDMARDs	18 (27.3)	29 (24.8)	77 (33.9)	98 (28.0)	53 (46.1)	57 (21.3)	34 (29.3)	11 (23.4)	<0.001
NSAIDs	24 (36.4)	42 (35.9)	118 (52.0)	169 (48.3)	63 (54.8)	118 (44.0)	64 (55.2)	26 (55.3)	0.008
Systemic glucocorticoids	21 (31.8)	12 (10.3)	53 (23.3)	68 (19.4)	40 (34.8)	26 (9.7)	22 (19.0)	8 (17.0)	<0.001
Analgesics	8 (12.1)	7 (6.0)	24 (10.6)	47 (13.4)	16 (13.9)	20 (7.5)	12 (10.3)	5 (10.6)	0.198
Opioid drugs	6 (9.1)	2 (1.7)	9 (4.0)	13 (3.7)	4 (3.5)	6 (2.2)	2 (1.7)	2 (4.3)	0.181
Drugs for acid related disorders	4 (6.1)	4 (3.4)	18 (7.9)	25 (7.1)	8 (7.0)	15 (5.6)	9 (7.8)	7 (14.9)	0.314
Antiinfectives for systemic use	6 (9.1)	5 (4.3)	15 (6.6)	25 (7.1)	3 (2.6)	15 (5.6)	8 (6.9)	3 (6.4)	0.641
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	2 (3.0)	9 (7.7)	10 (4.4)	10 (2.9)	9 (7.8)	18 (6.7)	3 (2.6)	3 (6.4)	0.127
Thyroid therapy	1 (1.5)	3 (2.6)	10 (4.4)	20 (5.7)	6 (5.2)	11 (4.1)	10 (8.6)	3 (6.4)	0.363
Antidepressant drugs	4 (6.1)	3 (2.6)	11 (4.8)	10 (2.9)	1 (0.9)	12 (4.5)	4 (3.4)	0	0.319
Antihypertensive drugs	7 (10.6)	1 (0.9)	6 (2.6)	10 (2.9)	6 (5.2)	4 (1.5)	4 (3.4)	3 (6.4)	0.005
Eye antiinfectives and antiinflammatory agents	0	6 (5.1)	4 (1.8)	4 (1.1)	0	9 (3.4)	0	0	0.010
Antiepileptic drugs	0	0	8 (3.5)	5 (1.4)	1 (0.9)	6 (2.2)	0	0	0.082
Psycholeptic drugs	1 (1.5)	1 (0.9)	4 (1.8)	2 (0.6)	1 (0.9)	7 (2.6)	3 (2.6)	0	0.444
Antithrombotic agents	3 (4.5)	1 (0.9)	2 (0.9)	4 (1.1)	4 (3.5)	1 (0.4)	0	0	0.027
Drugs used in diabetes	1 (1.5)	1 (0.9)	2 (0.9)	3 (0.9)	2 (1.7)	2 (0.7)	2 (1.7)	1 (2.1)	0.953
Antiglaucoma preparations and miotics	0	0	5 (2.2)	0	0	2 (0.7)	1 (0.9)	0	–
Drugs affecting bone structure and mineralisation	0	0	1 (0.4)	1 (0.3)	0	0	0	0	–
Lipid modifying agents	1 (1.5)	0	0	1 (0.3)	0	0	0	0	–

The values are N (%) unless indicated otherwise.
*Univariable analysis of variance for continuously distributed parameters or χ^2 test for categorical parameters.
bDMARD, biological DMARD; DMARD, disease-modifying antirheumatic drug; ErA, Enthesitis-related arthritis; ExtOA, Extended oligoarthritis; NSAIDs, non-steroidal antiinflammatory drugs; PersOA, persistent oligoarthritis; PsA, psoriatic arthritis; RF- PA, rheumatoid factor-negative polyarthritis; RF+ PA, RF-positive polyarthritis; sDMARD, synthetic DMARD; sJIA, systemic JIA; undiffA, undifferentiated arthritis.

Table 4 Outcome parameters related to the number of non-DMARD medications taken in the previous 6 months

Parameters	Patients w/o non-DMARD drugs	OR (95% CI)*	P value	Patients w 1 or 2 non-DMARD drugs (reference)	Patients w ≥3 non-DMARD drugs	OR (95% CI)*	P value
n	443			565	298		
No of non-DMARD medicines per patient	0			1.4 (0.5)	4.1 (1.3)		
Age, years	23.2 (3.7)	1.00 (0.96 to 1.03)	0.790	23.3 (4.0)	24.5 (4.8)	1.07 (1.04 to 1.11)	<0.001
Female, N (%)	253 (57.1%)	0.59 (0.46 to 0.77)	<0.001	391 (69.2%)	242 (81.2%)	1.92 (1.37 to 2.70)	<0.001
Disease duration, years	13.4 (5.3)	0.99 (0.97 to 1.01)	0.293	13.7 (5.7)	15.8 (7.2)	1.06 (1.03 to 1.08)	<0.001
Patient-reported disease activity, (NRS 0–10)	1.9 (1.9)	0.77 (0.72 to 0.82)	<0.001	2.9 (2.2)	4.0 (2.3)	1.22 (1.14 to 1.29)	<0.001
Patient-reported pain, (NRS 0–10)	1.6 (1.9)	0.77 (0.72 to 0.82)	<0.001	2.7 (2.3)	3.9 (2.6)	1.21 (1.14 to 1.28)	<0.001
Patient-reported fatigue, (NRS 0–10)	2.4 (2.5)	0.89 (0.85 to 0.94)	<0.001	3.1 (2.6)	4.5 (2.8)	1.19 (1.13 to 1.25)	<0.001
HAQ total score (range 0–3)	0.1 (0.3)	0.33 (0.22 to 0.49)	<0.001	0.3 (0.5)	0.6 (0.7)	2.62 (2.04 to 3.37)	<0.001
Patient-reported HRQoL, SF-36, mental component summary score	50.7 (8.6)	1.02 (1.01 to 1.03)	0.004	49.0 (9.6)	48.0 (10.1)	0.99 (0.98 to 1.00)	0.147
Patient-reported HRQoL, SF-36, physical component summary score	51.5 (8.0)	1.06 (1.05 to 1.08)	<0.001	47.0 (9.6)	39.4 (11.7)	0.94 (0.93 to 0.95)	<0.001
Time from symptom onset to first bDMARD in years	4.8 (4.0)	0.97 (0.94 to 1.00)	0.086	5.3 (4.2)	6.3 (4.8)	1.05 (1.01 to 1.09)	0.005

The values are Mean (SD) unless indicated otherwise.
*OR from multinomial logistic regression in order to compare each parameter separately with the reference group 'patients w 1 or 2 non-DMARD drugs'.
bDMARD, biological disease modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; HRQoL, Health-related quality of life; NRS, Numerical Rating Scale; SF-36, Short Form-36; w, with; w/o, without.

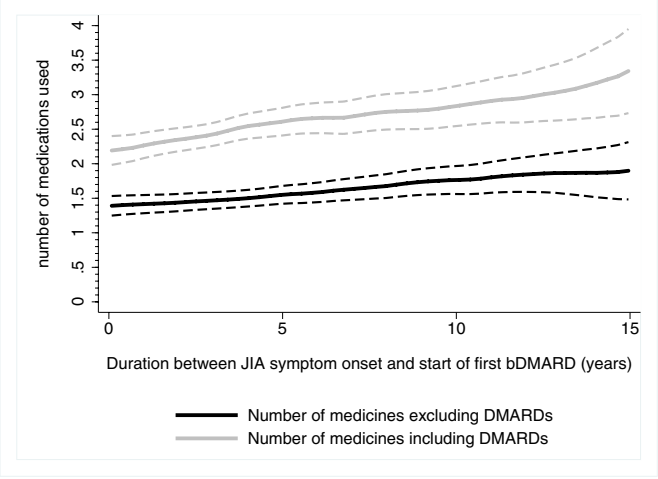

Figure 1 Number of medicines used (with and without DMARDs) in adulthood by duration between JIA symptom onset and start of first bDMARD therapy. bDMARDs, biological disease-modifying antirheumatic drugs; JIA, juvenile idiopathic arthritis.

three groups, the mean non-DMARD drug use was 1.5±1.7, with approximately half (643, 49.2%) taking non-DMARD medications. In the group of patients with ≥3 non-DMARD medicines, 57 (19.1%) patients were not receiving DMARD therapy. In general, the number of non-DMARD medicines showed significant associations with the selected outcomes, the higher the number of non-DMARDs was the worse the outcomes (online supplemental table 3).

Medication use by the time from symptom onset to first bDMARD start

The longer the time interval between the onset of JIA and the start of treatment with bDMARDs, the higher the average number of medications taken in adulthood was, including or excluding DMARDs, respectively (figure 1).

Patients with a late bDMARD start (group C) used 1.8±1.9 non-DMARD drugs, while patients with an early start (Group A) used 1.3±1.6. Approximately 80% of group C patients reported taking s/bDMARDs, while 64% of those in Group A used s/bDMARDs. The comparisons of the three groups were propensity score adjusted. Nevertheless, significant differences remained in mean age and disease duration among the three groups.

The use of specific drugs at follow-up in the three groups with early, medium or late bDMARD start is shown in online supplemental table 4. Group C patients reported significantly more frequent use of s/bDMARDs ($p<0.001$) and systemic glucocorticoids ($p=0.028$) than patients in Group A. In addition, the use of antidepressants differed significantly between these two groups ($p=0.022$).

A subgroup analysis showed that patients with sJIA and late onset of bDMARDs were most likely to be taking systemic glucocorticoids (n=15, 60%). In addition, the use of antihypertensives was reported by six (24%) of these patients, and pain treatment with opioids was reported by five (20%).

The comparison of medication use by disease onset (prebiological vs biological era) revealed that patients with disease onset in the biological era used significantly fewer bDMARDs, sDMARDs, NSAIDs, glucocorticoids, opioid drugs, antidepressants and antihypertensive drugs at follow-up than patients with disease onset before 2000 (online supplemental table 5).

Antidepressant and/or opioid consumption

At the last follow-up, 6% of patients reported antidepressant and/or opioid use (45 antidepressant use, 44 opioid drug use and 10 used both). Table 5 shows the characteristics of patients taking antidepressants or opioids. Considering the entire observation period in JUMBO of 4.5 years, 9.0% had taken an antidepressant and 110 (8.4%) had taken opioid drugs. Patients taking antidepressants and/or opioids had received bDMARDs an average of 2 years later than those not taking these medications.

DISCUSSION

This analysis revealed a tremendous medication burden in young adults treated with DMARDs for JIA. Women, patients with RF+ polyarthritis and sJIA, as well as those with a late start of bDMARD therapy, were particularly affected. Approximately one in four study participants was subject to polypharmacy. The data also show that the early initiation of therapy with biologics is associated with a lower medication burden in adulthood, with a reduced need for medications in general and a reduced need for DMARDs, systemic glucocorticoids and antidepressants in particular. Reduced use of glucocorticoids, in turn, may prevent comorbidities such as hypertension; a significant association between antihypertensive therapy and duration of exposure to systemic glucocorticoids has been demonstrated.

The consideration of patient-reported information has become a standard procedure in clinical practice and research to correctly evaluate the patient's response to therapy and their health.[26] In contrast, there have been few reports on self-reported medications in JIA. In long-term follow-up studies, data on medication use collected from patients in interviews/surveys were considered, as in the studies by Glerup *et al* and Selvaag.[2 5] Studies on the validity of medication self-reports have shown that self-reports have moderate to excellent agreement with pharmacy records and prescription data.[16 27–29] In JuMBO, patients indicated at each visit what medications they had taken in the previous 6 months. This self-reporting has been an important source of information and helped identify comorbidities, as reported medications sometimes indicated previously unknown comorbidities, which could then be confirmed after queries to the physicians. In agreement with Solomon *et al*,[16] we believe that these data are a valuable complement to

Table 5 Characteristics of patients reporting use of antidepressant drugs (N06A) or opioid consumption (N02A) at last follow-up

Parameters	No use of antidepressants or opioids	Opioid consumption	Use of antidepressants
n	1227	44*	45*
No of medicines per patient, (incl. DMARD)	2.2 (2.0)	5.8 (1.8)	5.1 (2.4)
Age, years	23.0 (4.0)	25.0 (5.3)	23.7 (4.8)
Female, N (%)	827 (67.4)	32 (72.7)	36 (80.0)
Disease duration, years	13.4 (5.9)	17.9 (7.3)	15.6 (7.4)
Patient-reported disease activity (NRS 0–10)	2.7 (2.2)	5.5 (1.9)	4.5 (2.1)
Patient-reported pain (NRS 0–10)	2.5 (2.3)	5.5 (2.0)	4.5 (2.5)
Patient-reported fatigue (NRS 0–10)	3.0 (2.7)	6.2 (2.3)	5.5 (2.4)
HAQ total score (range 0–3)	0.25 (0.47)	1.2 (0.76)	0.72 (0.78)
Patient-reported HRQoL, SF-36, mental component summary score	49.7 (9.4)	45.9 (11.1)	39.9 (10.9)
Patient-reported HRQoL, SF-36, physical component summary score	47.6 (10.3)	31.0 (9.9)	36.7 (11.4)
Time from symptom onset to first bDMARD in years	5.3 (4.3)	7.3 (5.1)	7.4 (4.9)
Current treatment with DMARD, N (%)	774 (63.1)	36 (81.8)	35 (77.8)
Current treatment with synthetic DMARDs, N (%)	369 (30.1)	32 (52.3)	20 (44.4)
Current treatment with biological DMARD, N (%)	696 (56.8)	31 (70.6)	31 (68.8)
NSAIDs, N (%)	566 (46.1)	35 (79.5)	31 (68.9)
Systemic glucocorticoids, N (%)	216 (17.6)	24 (54.5)	16 (35.6)

The values are Mean (SD) unless indicated otherwise.
*Ten patients were taking both antidepressants and opioids, contributing to both columns.
DMARD, disease modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; HRQoL, health-related quality of life; NRS, Numerical Rating Scale; NSAIDS, non-steroidal anti-inflammatory drugs; SF-36, Short Form-36.

physician-reported data and provide a better appraisal of the overall burden of disease.

The patient population in JuMBO represents one of the largest prospectively observed cohorts of adults with JIA. Participants have all been treated with DMARDs, most still at follow-up, and generally have a long-term need for rheumatological care. In this group of severely affected patients, only 18% reported no medication use at all at the last follow-up. On average, patients used 2.4 medications, including DMARDs, 14 years after disease onset, and almost a quarter used three or more medications regardless of DMARDs. As expected, patients with polypharmacy had a significantly higher burden of disease than those who needed fewer medications. Their disease activity, pain, fatigue and functional limitations were higher, and their physical health was worse than those of patients taking fewer medications. This finding is not unexpected; data from the Medical Expenditure Panel Survey have also previously shown a significant association between polypharmacy and lower physical health scores among adults with arthritis.[30]

On average, women took more medications than men. Regarding individual substance groups, they were significantly more likely to take synthetic DMARDs, NSAIDs, glucocorticoids, analgesics, antithyroid agents and antithrombotics than men. Possible reasons for this likelihood include the overall higher pain sensitivity of women compared with men,[31] the preponderance of women in JIA categories with a comparatively high need for NSAIDs/pain medications (eg, polyarticular JIA) and additional autoimmune diseases (such as thyroiditis).[32] The data of this study also suggest that women with JIA, regardless of JIA category, tend to have higher disease activity and a higher subjectively perceived disease burden than men.

Significant differences were also found in medication use among patients with different JIA categories. Patients with RF+ polyarthritis were those with the highest mean number of medications, followed by those with sJIA and extended oligoarthritis. Patients with RF+ polyarthritis and sJIA also most frequently reported the use of systemic glucocorticoids as well as antihypertensives and anticoagulants. Associations are obvious. Hypertension is a well-documented adverse effect of glucocorticoids, with the risk related to the cumulative dose of glucocorticoids.[33–36] In this study, antihypertensive treatment was associated with the duration of glucocorticoid treatment, and half of the patients receiving antihypertensive treatment were concomitantly treated with systemic corticosteroids at follow-up. Glucocorticoid users also have a

higher risk of venous thromboembolism, which has been demonstrated in a large population-based case–control study using nationwide databases[37] and to which this study already supports despite the small case numbers. Patients with sJIA were among those JIA patients in the prebiological era who required glucocorticoids most frequently and for the longest duration and were at greatest risk for disease-related or treatment-related sequelae.[38 39] In this study, this risk is somewhat reflected in the medication burden of sJIA patients who received bDMARDs late in the disease course. Those patients were more likely to use glucocorticoids, NSAIDs, analgesics, including opioids, antidepressants, antihypertensives and antithrombotics at follow-up than those treated with bDMARDs within the first 2 years of illness. The approval of the IL-6 and IL-1 inhibitors tocilizumab in 2011, canakinumab in 2013, and, most recently, anakinra in 2018 was a breakthrough in the treatment of sJIA patients.[40] Meanwhile, sJIA patients have the highest drug-free remission rate of all JIA patients,[5] which is not yet reflected at a DMARD rate of 68% at follow-up in this study.

The study results suggest, however, that early use of potent DMARDs may reduce drug and disease burden in adulthood, supporting the currently recommended treat-to-target approach in JIA.[41] It was shown that, in particular, patients who started bDMARDs late in the disease course were among those who exhibited polypharmacy and required antidepressants and opioids.

Of course, self-reported medication use does not allow for reliable estimates of the prevalence of specific comorbidities, as noted by Vaes *et al*.[28] The group of antihypertensives, for example, consists of several drug categories. Therefore, it must be taken into account that individual drugs in this group may also have been used for other purposes, for example, other heart diseases, such as cardiac arrhythmias. However, a high rate of other cardiac diseases seems unlikely in this young patient population, considering data on the self-reported comorbidities.[28]

Moreover, studies from other areas of medicine suggest that some patients do not accurately report the long-term use of treatment.[16 42] This limitation may also have been the case in this study. For example, only 3.4% of patients reported taking antidepressants at the last visit, compared with 9% over the entire observation period in JuMBO. However, not all patients with depression are treated regularly with drugs. From health insurance data, we know that only half the patients with axial spondyloarthritis with depression receive pharmacological treatment.[43] Therefore, when estimating the prevalence of comorbidities, patient and physician reports of comorbidities must also be considered.

In addition to the above limitations, there are others that must be kept in mind when interpreting the study data. Our study population included only patients who received DMARDs in childhood or adolescence and therefore proportionately fewer patients with oligoarthritis. Therefore, the results are not generalisable to the entire JIA population. On the other hand, it is a strength of this study that a large group of severely affected JIA patients with high care needs could be recruited over a period of more than ten years at DMARD initiation, prospectively observed and interviewed in adulthood to uncover strategies to improve prognosis for these patients at high risk for sequelae.

It is also important to remember that self-reported data is subject to recall error and bias, and patients may be less willing to disclose details about certain medications than other.[44] In this study, the data collection period was 6 months, which may be considered long. However, Hafferty *et al* found better agreement between medication self-report and prescription data for the 6 month window than for the 3-month window. For DMARD use, there was good agreement with reports from treating rheumatologists.

In summary, approximately one-quarter of patients with a DMARD-necessitating JIA, particularly those starting bDMARD therapy later in the disease course, have a high medication burden in adulthood. In this study, self-reported medication use indicated treatment- and/or disease-related sequelae or comorbidities and provided valuable information on the long-term prognosis of JIA, which in turn may contribute to further outcome improvement. Further analysis of comorbidities is needed to provide better insight into the burden of disease in adults with JIA.

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