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Original article

Pharmacological treatment patterns in patients with juvenile idiopathic arthritis in the Netherlands: a real-world data analysis

Michelle M. A. Kip [1,2], Sytze de Roock[2,3], Gillian Currie[4,5,6,7], Deborah A. Marshall [4,6,7], Luiza R. Grazziotin[4], Marinka Twilt[6,8], Rae S. M. Yeung[9], Susanne M. Benseler [6,8], Sebastiaan J. Vastert[2,3,10], Nico Wulffraat[2,3,10], Joost F. Swart [2,3,10,*] and Maarten J. IJzerman[1,11,*]

Abstract

Objective. To investigate medication prescription patterns among children with JIA, including duration, sequence and reasons for medication discontinuation.

Methods. This study is a single-centre, retrospective analysis of prospective data from the electronic medical records of JIA patients receiving systemic therapy aged 0–18 years between 1 April 2011 and 31 March 2019. Patient characteristics (age, gender, JIA subtype) and medication prescriptions were extracted and analysed using descriptive statistics, Sankey diagrams and Kaplan–Meier survival methods.

Results. Over a median of 4.2 years follow-up, the 20 different medicines analysed were prescribed as monotherapy ($n = 15$) or combination therapy ($n = 48$ unique combinations) among 236 patients. In non-systemic JIA, synthetic DMARDs were prescribed to almost all patients (99.5%), and always included MTX. In contrast, 43.9% of non-systemic JIA patients received a biologic DMARD (mostly adalimumab or etanercept), ranging from 30.9% for oligoarticular persistent ANA-positive JIA, to 90.9% for polyarticular RF-positive JIA. Among systemic JIA, 91.7% received a biologic DMARD (always including anakinra). When analysing medication prescriptions according to their class, 32.6% involved combination therapy. In 56.8% of patients, subsequent treatment lines were initiated after unsuccessful first-line treatment, resulting in 68 unique sequences. Remission was the most common reason for DMARD discontinuation (44.7%), followed by adverse events (28.9%) and ineffectiveness (22.1%).

Conclusion. This paper reveals the complexity of pharmacological treatment in JIA, as indicated by: the variety of mono- and combination therapies prescribed, substantial variation in medication prescriptions between subtypes, most patients receiving two or more treatment lines, and the large number of unique treatment sequences.

Key words: JIA, DMARD, biologicals, treatment

CLINICAL SCIENCE

Introduction

JIA is defined as arthritis of unknown aetiology, presenting in children <16 years old and persisting for ≥6 weeks [1]. It is one of the most prevalent chronic inflammatory childhood diseases, affecting ∼1 in 1000 children [2–4]. Early recognition and effective management can minimize the disease burden, including pain and functional disability, both during childhood and later in life [5]. More specifically, the main goal is to achieve long-term disease remission [6]. The greater availability of DMARDs, and in particular the development of biologic DMARDs (bDMARDs), in the past two decades, have

[1]Department of Health Technology and Services Research, Faculty of Behavioural, Management and Social Sciences, Technical Medical Centre, University of Twente, Enschede, [2]Department of Pediatric Rheumatology, Division of Paediatrics, University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, [3]Faculty of Medicine, Utrecht University, Utrecht, The Netherlands, [4]Department of Community Health Sciences, [5]Department of Paediatrics, Cumming School of Medicine, [6]Alberta Children's Hospital Research Institute, [7]Department of Medicine, [8]Division of Rheumatology, Department of Pediatrics, Alberta Children's Hospital, Cumming School of Medicine, University of Calgary, Calgary, Alberta, [9]Division of Rheumatology, The Hospital for Sick Children, Department of Paediatrics, Immunology and Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada, [10]European Reference Network RITA (rare Immunodeficiency Autoinflammatory and Autoimmune Diseases Network) and [11]Melbourne School of Population and Global Health, University of Melbourne, Parkville, Melbourne, Australia

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Correspondence to: Maarten J. IJzerman, Department of Health Technology and Services Research, Faculty of Behavioural, Management and Social Sciences, Technical Medical Centre, University of Twente, PO Box 217, 7500 AE Enschede, The Netherlands. E-mail: m.j.ijzerman@utwente.nl

*Joost F. Swart and Maarten J. IJzerman contributed equally to this study.

Rheumatology key messages

- This paper illustrates the complexity of pharmacological treatment decisions in JIA.
- Sixty-eight unique treatment sequences were observed among 236 patients, with 56.8% receiving two or more treatment lines.
- The strong heterogeneity of JIA disease manifestation highlights the need for a treat-to-target approach.

significantly enhanced treatment opportunities in JIA. Despite this, remission rates off medication range from only 7% within 1.5 years to 47% by 10 years after diagnosis [6].

The International League of Associations for Rheumatology (ILAR) distinguishes seven JIA subtypes which differ in clinical and laboratory features as well as in disease severity [1]. In addition, even within subtype, there is substantial variation in disease severity and treatment response [1, 7–10]. Treat-to-target strategies, adjusted to the patient's disease activity, subtype and response to previous treatment(s), are already applied in adults with RA [11–13] and are also needed in JIA [13–15]. This could however result in earlier use of bDMARDs in these patients. Since bDMARDs cost ~20–500 times as much as synthetic DMARDs (sDMARDs) like MTX [16], their benefits in terms of reducing time to remission and long-term disability should be considered relative to their costs [17–19].

Although a few studies in the field of JIA reported improved disease control due to early bDMARD use [14, 17, 18, 20], this evidence is scarce and mostly limited to a particular JIA subtype and/or a specific bDMARD. Insight into patients switching between sDMARDs and bDMARDs, the use of different types of sDMARDs and bDMARDs, and reasons for switching, is lacking. Also, the use of sDMARDs and bDMARDs in relation to other pharmacological treatment options in JIA, including IA injections as well as systemic steroids, is unknown. The current study therefore aims to provide insight into these medication prescription patterns, using data from a real-world cohort of JIA patients. More specifically, we assessed the types and number of systemic steroids, sDMARDs and bDMARDs prescribed, the sequence in which they were prescribed over the follow-up period, the time between JIA diagnosis and their prescription, as well as reasons for switching to another type of sDMARD or bDMARD, in relation to the JIA subtype.

Methods

Data sources and extraction

This study involved a retrospective analysis of data prospectively collected in the electronic medical records from the paediatric rheumatology department of the tertiary referral centre Wilhelmina Children's Hospital (Utrecht, The Netherlands). These data were extracted using a previously developed research data platform [15], resulting in a comprehensive set of within-hospital databases connected through a unique, de-identified, patient number. The institutional review board classified the use of data from the research data platform as exempt from the Medical Research Involving Human Subjects Act (14/684). This study was conducted according to Good Clinical Practice guidelines and the declaration of Helsinki [21], and was approved by the ethical committee of the faculty of Behavioural, Management and Social Sciences of the University of Twente (no. 190216).

Data selection

This analysis includes data from patients aged 0–18 years with a diagnosis of JIA, treated in the Wilhelmina Children's Hospital and who received systemic pharmaceutical treatment (sDMARDs, bDMARDs and/or systemic steroids) between 1 April 2011 and 31 March 2019. Patients were excluded when they: were diagnosed with JIA before 1 April 2011; only received IA injections without systemic pharmaceutical treatment within this time period; were diagnosed with idiopathic uveitis (i.e. uveitis without arthritis) or undifferentiated JIA; turned 18 years of age before 1 April 2011; were not primarily treated in the Wilhelmina Children's Hospital because they (for example) only came for a second opinion; had major comorbidities (such as IBD) alongside their JIA; received treatment as part of a pharmaceutical trial which they would not have received outside the trial setting (regardless when this occurred); already received a sDMARD and/or bDMARD for >30 days prior to their JIA diagnosis; or had a follow-up <1 year (supplementary Fig. S1, available at *Rheumatology* online). The starting date of 1 April 2011 was chosen as the data were not available in electronic form before this date, and because the rapid evolution in JIA treatment strategies makes data obtained >10 years ago no longer reflective of current clinical practice. Also, as the availability of healthcare resource use data was strongly limited after the patients were transferred to adult care, we could not include data after their 18th birthday.

Analysis

The date of JIA diagnosis was set as starting date of the analysis. Patients with oligoarthritis were subdivided according to ANA status. All analyses were performed using R (version 4.0.3), and the packages lubridate, tidyverse, networkD3 and Table 1 [22–27].

Types and number of distinct systemic steroids, sDMARDs and bDMARDs prescribed

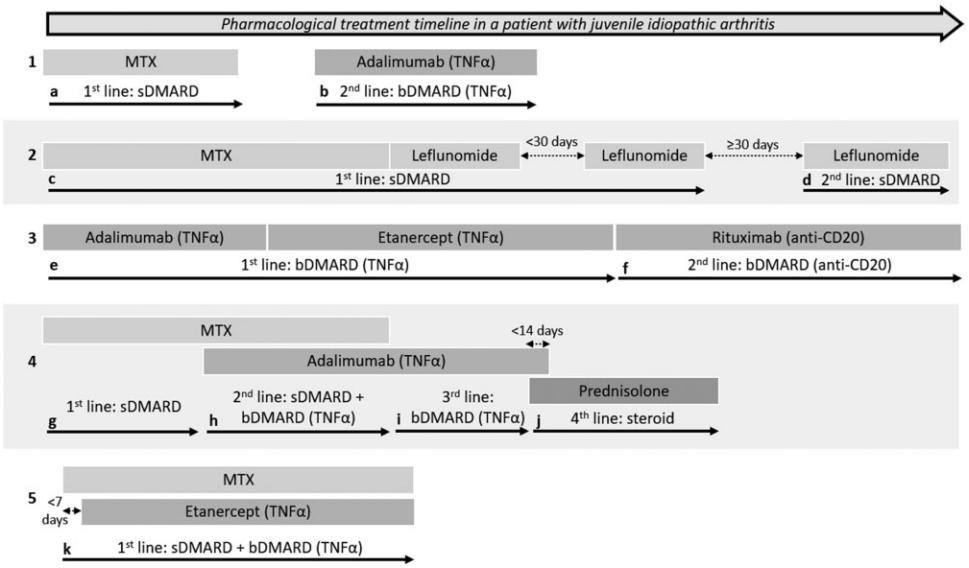
The medicines prescribed to these patients were categorized into the following classes: (i) systemic steroids (prednisolone, dexamethasone and methylprednisolone), (ii) sDMARDs (oral and subcutaneous MTX, LEF, HCQ, MMF, AZA and SSZ), and (iii) bDMARDs (subcutaneous abatacept, adalimumab, anakinra, canakinumab, etanercept, golimumab, infliximab and rituximab, and intravenous and subcutaneous tocilizumab). In addition, IA injections were included for patients who received at least one of the abovementioned systemic therapies.

Analysis of treatment lines

To get insight into which classes of medicines (i.e. systemic steroids, sDMARDs and bDMARDs) were prescribed to JIA patients, either in monotherapy or combination therapy, and in which sequence over a patient's treatment course, we categorized all medication prescriptions into distinct lines of treatment. For this, bDMARDs were classified according to their mechanism of action into anti-CD20 (rituximab), anti-IL-1 (anakinra and canakinumab), anti-IL-6 (tocilizumab), CTLA-4 (abatacept) and TNF-α inhibitors (adalimumab, etanercept, golimumab and infliximab).

Subsequently, the following choices were made in consultation with two paediatric rheumatologists to define lines of treatment: (i) switching to a medicine from a different class (e.g. from sDMARD to bDMARD), or to a bDMARD with a different mechanism of action (e.g. from TNF-α to anti-CD20), regardless of the time lag between stopping and starting, is considered a new line of treatment (lines a→b and e→f, respectively, in Fig. 1); (ii) switching to another medicine within the class of sDMARDs [e.g. from MTX to LEF (line c)], or from one bDMARD to another bDMARD with the same mechanism of action [i.e. from adalimumab to etanercept (line e)] is not considered a new line of treatment; (iii) if the same medicine, or a sDMARD from the same class, or a bDMARD with the same mechanism of action, is stopped and restarted after $\geq$30 days (e.g. because of a disease flare) this is considered a new line of treatment (lines c→d); (iv) medicines from different classes or with a different mechanism of action with overlapping prescription periods of $\geq$14 days are defined as combination therapy which, together, constitute a single line of treatment (line h), whereas medicines which overlap $<$14 days are considered as distinct lines of monotherapy

Fig. 1 Definition of treatment lines, visualized using five hypothetical sequences of medication prescribed to JIA patients



Description of treatment sequences: (1) first-line sDMARD monotherapy (MTX) (a), stopping $\geq$30 days, then continue with a bDMARD (TNF-α inhibitor, i.e. adalimumab) as second-line treatment (b); (2) first-line sDMARD capturing the use of MTX, a switch to LEF (without time lag), and discontinuing LEF but re-starting $<$30 days (c), and re-starting LEF after discontinuing $\geq$30 days (d); (3) first-line bDMARD (TNF-α) represented by adalimumab treatment and subsequently etanercept (e), following a switch to a different type of bDMARD (i.e. rituximab), which is therefore defined as second-line treatment (f); (4) MTX monotherapy as first-line treatment (g), followed by the addition of a bDMARD (adalimumab) which leads to second-line (combination) therapy (h), and stopping MTX leads to bDMARD monotherapy as third-line treatment (i). Although prednisolone is started simultaneously with adalimumab, this overlap is $<$14 days, and is therefore not defined as combination therapy (j). (5) Adding etanercept to MTX monotherapy $\leq$7 days of starting MTX is considered as first-line combination therapy (k). bDMARD: biologic DMARD; sDMARD: synthetic DMARD.

(line j); and (v) when patients start two medicines from different classes or with a different mechanism of action in ≤7 days, which are prescribed simultaneously for ≥14 days, this is considered a single line of combination therapy (line k).

Time to bDMARD and sDMARD initiation

Kaplan–Meier methods were used to account for between-patient differences in the duration of follow-up captured in the database. The cumulative proportion of patients initiating sDMARDs and bDMARDs annually was estimated over a 3-year period, using the date of JIA diagnosis as index date. Inverted Kaplan–Meier curves were created to calculate median times to start sDMARD and bDMARD treatment, stratified by JIA subtype. Patients were censored when they left the cohort due to any of the abovementioned reasons.

Reasons for medication (dis)continuation

Reasons for medication discontinuation were prospectively reported by the treating paediatric rheumatologist and extracted from the research data platform. These reasons included ineffectiveness (including loss of efficacy), remission, adverse events (including intolerance) and other (patient preferred or decided to stop). Kaplan–Meier plots were created to visualize censoring due to patients reaching the end of follow-up while their medication was not yet discontinued.

Results

A total of 236 patients met the inclusion criteria. The median follow-up period was 4.2 years [interquartile range (IQR) 2.5–5.8]. The median age at JIA diagnosis was 9.9 years (IQR 3.9–13.7) and 82 patients (34.7%) were male (Table 1). Polyarticular RF-negative JIA was the most common subtype ($n = 60$, 25.4%).

Table 1 Overview of patient characteristics

Number of patients, *n*	236
Age at JIA diagnosis in years, median (IQR)	9.9 (3.9–13.7)
Duration of follow-up in years, median (IQR)	4.2 (2.5–5.8)
Gender, *n* (%)	
Male	82 (34.7)
JIA subtype, *n* (%)	
Oligoarticular persistent JIA	82 (34.7)
ANA-positive	55 (23.3)
ANA-negative	27 (11.4)
Polyarticular JIA	71 (30.1)
RF-negative	60 (25.4)
RF-positive	11 (4.7)
Extended oligoarticular JIA	21 (8.9)
Enthesitis-related JIA	31 (13.1)
Systemic JIA	24 (10.2)
PsA	7 (3.0)

IQR: interquartile range.

Types and number of systemic steroids, sDMARDs and bDMARDs prescribed

Of the 236 patients who were prescribed systemic JIA treatment during follow-up, 37 (15.7%) were prescribed at least once a systemic steroid, 216 (91.5%) a sDMARD and 115 (48.7%) a bDMARD (Table 2). Among non-systemic JIA patients, sDMARDs were the most common medicine prescribed (211 out of 212 patients, 99.5%). The remaining patient only received systemic steroids. All 211 patients had MTX prescribed at some point during follow-up, and only 30 of these patients also had another type of sDMARD prescribed (14.2%). From all 212 non-systemic JIA patients, 93 (43.9%) had a bDMARD prescribed during follow-up. The TNF-α inhibitors adalimumab and etanercept were most commonly prescribed, with 66 (31.1%) and 44 (20.8%), respectively, out of 212 patients receiving it during follow-up. Out of the 93 non-systemic JIA patients who had a bDMARD prescribed, 65 patients (69.9%) received only one type of bDMARD. When considering systemic JIA patients, bDMARDs were the most common systemic therapy, which were prescribed to 22 out of 24 patients (91.7%) during follow-up. All 22 patients were prescribed anakinra (anti-IL-1) as first bDMARD. Tocilizumab (anti-IL-6) and canakinumab (anti-IL-1) were prescribed to five (20.8%) and three (12.5%) patients, respectively. Only 3 out of 24 (12.5%) patients received MTX. The maximum number of different types of systemic steroids, sDMARDs and bDMARDs (regardless of their mechanism of action) prescribed to all JIA patients was two ($n = 3$, 1.3%), three ($n = 3$, 1.3%) and four ($n = 2$, 0.8%), respectively.

Of all 236 patients, 96 patients (40.7%) received at least one IA steroid injection. In total, 213 IA steroid injections were administered. With 36 out of 55 patients ($n = 65.5\%$), oligoarticular persistent ANA-positive was the subtype with most JIA patients receiving IA steroid injections (supplementary Table S1, available at *Rheumatology* online). As joint injections involve a singular or intermittent (i.e. non-continuous) administration of medication, as opposed to systemic therapy, these injections were excluded from the remainder of the analysis.

Analysis of treatment lines

The 20 different types of systemic therapies included in the analysis (i.e. 3 types of systemic steroids, 7 sDMARDs and 10 bDMARDs) were prescribed as monotherapy ($n = 15$) or combination therapy ($n = 48$ unique combinations). A detailed overview is provided in supplementary Tables S2a and S2b, available at *Rheumatology* online. When categorizing all medicines according to their class and mechanism of action [i.e. steroids, sDMARDs or bDMARDs (anti-CD20, anti-IL-1, anti-IL-6, CTLA4 and TNF)], 20 unique mono- or combination therapies were identified (supplementary Table S3, available at *Rheumatology* online). This categorization

Table 2 Overview of sDMARD, bDMARD and steroid prescriptions

	Enthesitis related JIA (*n* = 31)	Extended oligoart. JIA (*n* = 21)	Oligoart. persistent JIA ANA– (*n* = 27)	Oligoart. persistent JIA ANA+ (*n* = 55)	Polyart. JIA RF– (*n* = 60)	Polyart. JIA RF+ (*n* = 11)	PsA (*n* = 7)	Systemic JIA (*n* = 24)	Overall (*n* = 236)
Systemic steroids (*n*, %)	3 (9.7)	5 (23.8)	1 (3.7)	5 (9.1)	13 (21.7)	3 (27.3)	0 (0.0)	7 (29.2)	37 (15.7)
Type of systemic steroids prescribed (*n*, %)									
Prednisolone	3 (9.7)	5 (23.8)	1 (3.7)	5 (9.1)	13 (21.7)	3 (27.3)	0 (0.0)	7 (29.2)	37 (15.7)
Methyl-prednisolone	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
Dexamethasone	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	1 (0.4)
Different types of systemic steroids prescribed (*n*, %)									
0	28 (90.3)	16 (76.2)	26 (96.3)	50 (90.9)	47 (78.3)	8 (72.7)	7 (100.0)	17 (70.8)	199 (84.3)
1	3 (9.7)	4 (19.0)	1 (3.7)	5 (9.1)	12 (20.0)	3 (27.3)	0 (0.0)	6 (25.0)	34 (14.4)
2	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (4.2)	3 (1.3)
sDMARDs (*n*, %)	31 (100.0)	21 (100.0)	26 (96.3)	55 (100.0)	60 (100.0)	11 (100.0)	7 (100.0)	5 (20.8)	216 (91.5)
Type of sDMARDs prescribed (*n*, %)									
MTX	31 (100.0)	21 (100.0)	26 (96.3)	55 (100.0)	60 (100.0)	11 (100.0)	7 (100.0)	3 (12.5)	214 (90.7)
LEF	2 (6.5)	1 (4.8)	5 (18.5)	6 (10.9)	3 (5.0)	1 (9.1)	0 (0.0)	0 (0.0)	18 (7.6)
SSZ	6 (19.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	8 (3.4)
Other	1 (3.2)	0 (0.0)	1 (3.7)	2 (3.6)	3 (5.0)	0 (0.0)	0 (0.0)	2 (8.3)	9 (3.8)
Different types of sDMARDs prescribed (*n*, %)									
0	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (79.2)	20 (8.5)
1	22 (71.0)	20 (95.2)	21 (77.8)	48 (87.3)	53 (88.3)	10 (90.9)	7 (100.0)	5 (20.8)	186 (78.8)
2	9 (29.0)	1 (4.8)	4 (14.8)	6 (10.9)	6 (10.0)	1 (9.1)	0 (0.0)	0 (0.0)	27 (11.4)
3	0 (0.0)	0 (0.0)	1 (3.7)	1 (1.8)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)
bDMARDs (*n*, %)	17 (54.8)	10 (47.6)	9 (33.3)	17 (30.9)	26 (43.3)	10 (90.9)	4 (57.1)	22 (91.7)	115 (48.7)
Type of bDMARDs prescribed (*n*, %)									
Adalimumab (TNF)	15 (48.4)	5 (23.8)	6 (22.2)	14 (25.5)	17 (28.3)	7 (63.6)	2 (28.6)	0 (0.0)	66 (28.0)
Etanercept (TNF)	5 (16.1)	8 (38.1)	4 (14.8)	6 (10.9)	14 (23.3)	5 (45.5)	2 (28.6)	0 (0.0)	44 (18.6)
Anakinra (anti-IL1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (91.7)	22 (9.3)
Tocilizumab (anti-IL6)	1 (3.2)	0 (0.0)	1 (3.7)	1 (1.8)	4 (6.7)	3 (18.2)	0 (0.0)	5 (20.8)	14 (5.9)
Golimumab (TNF)	0 (0.0)	0 (0.0)	2 (7.4)	0 (0.0)	3 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.1)
Other	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	1 (1.7)	1 (9.1)	0 (0.0)	3 (12.5)	6 (2.5)
Different types of bDMARDs prescribed (*n*, %)									
0	14 (45.2)	11 (52.4)	18 (66.7)	38 (69.1)	34 (56.7)	2 (18.2)	3 (42.9)	2 (8.3)	122 (51.7)
1	13 (41.9)	6 (28.6)	7 (25.9)	14 (25.5)	16 (26.7)	5 (45.5)	4 (57.1)	15 (62.5)	80 (33.9)
2	4 (12.9)	4 (1.09)	1 (3.7)	2 (3.6)	7 (11.7)	2 (18.2)	0 (0.0)	6 (25.0)	26 (11.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	3 (5.0)	2 (18.2)	0 (0.0)	1 (4.2)	7 (3.0)
4	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	2 (0.8)

This table shows the number and percentage of JIA patients who had systemic steroids, sDMARDs or bDMARDs prescribed during their follow-up period, as well as the number of different types of systemic steroids, sDMARDs or bDMARDs prescribed during this follow-up period, specified by JIA subtype. ANA–: ANA-negative; ANA+: ANA-positive; bDMARD: biologic DMARD, IQR: interquartile range; oligoart.: oligoarticular; polyart. polyarticular; RF-: RF-negative; RF+: RF-positive; sDMARD: synthetic DMARD.

was used to distinguish all medication prescriptions into lines of treatment. In this context, first-line treatment was defined as the first (combination of) medicines a patient receives after JIA diagnosis. Among the 236 patients included, 540 lines of treatment were identified, consisting of 364 monotherapy prescriptions and 176 combination therapies. Combination therapy involved combinations of either two ($n = 154$, 87.5%), three ($n = 21$, 11.9%) or four medicines ($n = 1$, 0.6%). The 236 patients received on average 2.3 lines of treatment (median $n = 2$) over a median of 4.2 years follow-up.

Most patients ($n = 190$, 80.5%) started with sDMARD monotherapy as first-line treatment, which was MTX in 185 out of 190 patients (97.4%). Twenty-seven out of 236 patients (11.4%) started with a bDMARD, including 20 systemic JIA patients who started with anti-IL-1 monotherapy (anakinra). The remaining seven patients had enthesitis-related JIA ($n = 6$) and polyarticular RF-negative JIA ($n = 1$). These patients started with etanercept monotherapy ($n = 1$), or combination therapy of MTX with a TNF-α inhibitor [adalimumab ($n = 4$) and etanercept ($n = 2$)]. The remaining 19 patients received combination therapy of a sDMARD and a systemic steroid ($n = 14$), or systemic steroid monotherapy ($n = 5$), as first-line treatment.

Consecutive lines of treatment were prescribed when first-line treatment was either ineffective, due to adverse events, or other causes. After first-line treatment ($n = 236$), 134 patients (56.8%) proceeded to second-line treatment, 76 (32.2%) to third-line treatment and 41 (17.4%) to fourth-line treatment. The maximum number of treatment lines observed in the dataset was 11 ($n = 1$).

Of all patients receiving sDMARDs as first-line monotherapy ($n = 190$, 80.5%), 84 patients (35.6%) stayed on this treatment during their entire follow-up period. Of these patients, 63 (26.7%) proceeded to a bDMARD as second-line treatment, either as monotherapy ($n = 11$, 17.5%) or combination therapy ($n = 52$, 82.5%). When considering the sequential lines of treatment prescribed, 65 unique treatment sequences were identified among the 236 patients included. Fig. 2 shows an overview of sequential treatments for the first four treatment lines.

Time to bDMARD and sDMARD initiation

Within 1 year after JIA diagnosis, the great majority of non-systemic JIA patients had a sDMARD prescribed, ranging from 76% (95% CI 62%, 85%) among oligoarticular persistent ANA-positive JIA, to 100% among polyarticular RF-positive JIA (Table 3). For oligoarticular persistent ANA-positive JIA, this percentage increases to 96% (95% CI 86%, 99%) after 3 years. The median time from JIA diagnosis until the first sDMARD prescription ranges from 0.003 years (95% CI 0.00, ∞, i.e. 1 day) in both polyarticular RF-positive JIA and PsA, to 0.23 years (95% CI 0.10, 0.47, i.e. 84 days) in oligoarticular persistent ANA-positive JIA. The prescription of bDMARDs in non-systemic JIA ranges from 9% (95% CI 1%, 16%) in oligoarticular persistent ANA-positive JIA to 73% (95% CI 28%, 90%) in polyarticular RF-positive JIA in the first year after JIA diagnosis. Within 3 years, these percentages increase to 21% (95% CI 9%, 32%) and 82% (95% CI 36%, 95%), respectively. The median time from JIA diagnosis until bDMARD prescription was 0.74 years ($n = 10$, 95% CI 0.27, ∞) for polyarticular RF-positive JIA, 0.96 years for enthesitis-related JIA ($n = 17$, 95% CI 0.57, ∞) and 2.37 years for PsA ($n = 4$, 95% CI 0.29, ∞). As <50% of patients from the other JIA subtypes received a bDMARD during follow-up, no median time to bDMARD initiation could be calculated. In systemic JIA, 92% (95% CI 69%, 98%) had a bDMARD prescribed during follow-up, with a median time between JIA diagnosis until bDMARD prescription of 0.01 year (95% CI 0.00, 0.04, i.e. 3 days). The corresponding Kaplan–Meier survival graphs are shown in supplementary Fig. S2, available at *Rheumatology* online. The time from JIA diagnosis until sDMARD and bDMARD prescription, by JIA subtype, is visualized in inverse Kaplan–Meier curves in supplementary Figs S3a and S3b, available at *Rheumatology* online.

Reasons for medication (dis)continuation

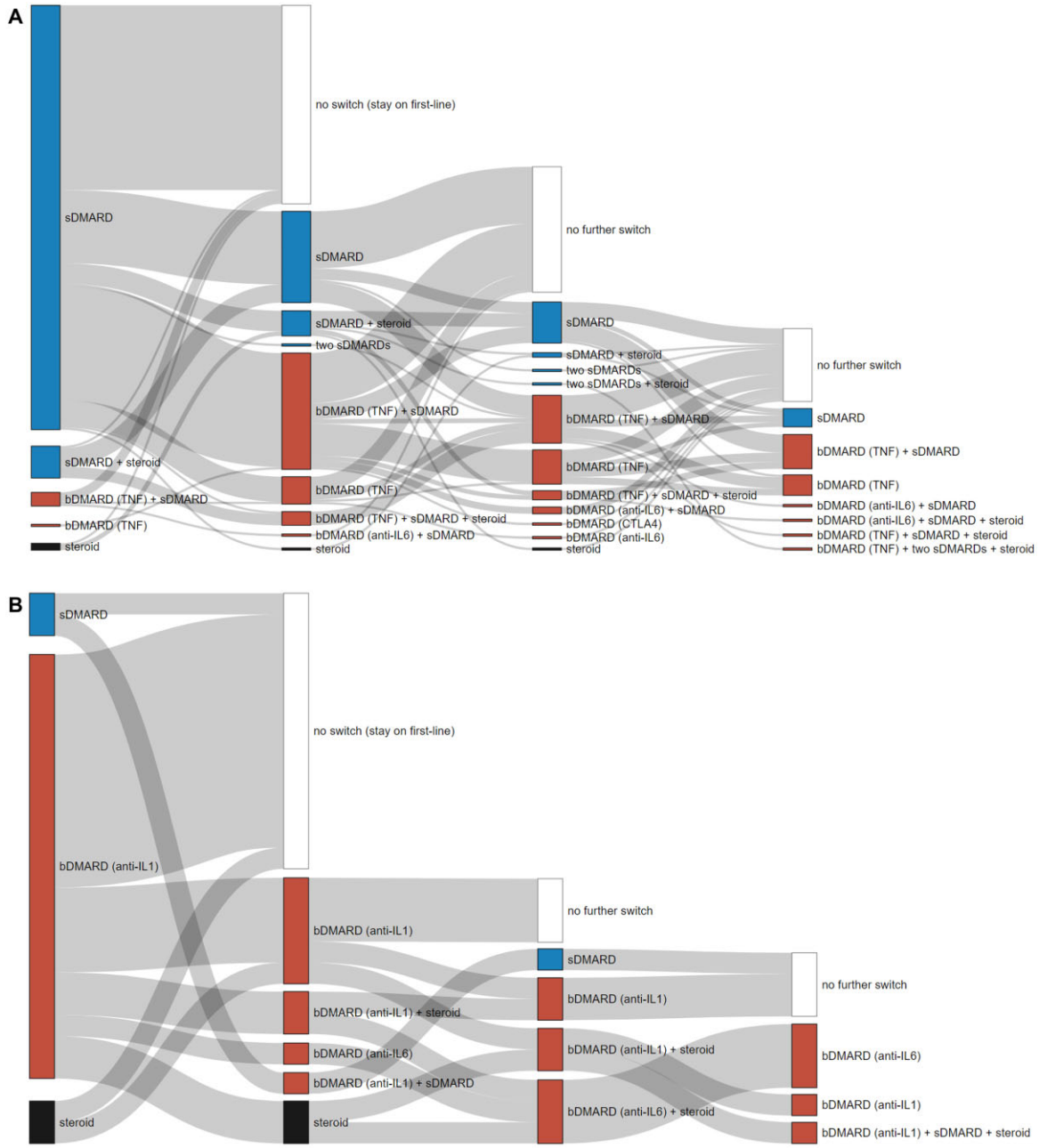
When considering the 551 individual medication prescriptions in the database, 156 (28.3%) were discontinued because remission was reached, 101 (18.3%), because of adverse events (including side effects like nausea), 77 (14.0%) because of ineffectiveness and 15 (2.7%) because the patient decided or preferred to stop. The remaining 202 medication prescriptions (36.7%) were not yet discontinued, indicating that 202 out of 236 patients (85.6%) had ongoing systemic steroid, sDMARD and/or bDMARD prescriptions at the end of their follow-up. Reasons for this involved: continuing medication after 31 March 2019, which is the end date of the database ($n = 142$, 70.3%); reaching the age of 18 ($n = 54$, 26.7%); and lost to follow-up ($n = 6$, 3.0%), for example due to transitioning to another hospital. Anti-IL-1 bDMARD was the type of medication that was most frequently discontinued because of remission ($n = 17$, 51.5%). MTX (oral and subcutaneous) was discontinued for remission in 94 out of 316 (29.7%) prescriptions, whereas 80 MTX prescriptions (25.3%) were discontinued because of adverse events (Table 4).

Discussion

This paper describes prescription patterns of sDMARDs, bDMARDs and steroids, stratified by JIA subtype, in a cohort of JIA patients diagnosed after 1 April 2011 with an episode of care that lasts at least 1 year, treated in the largest paediatric rheumatology centre in the Netherlands.

The results of this study have shown a large variability in medicines prescribed to JIA patients, major variations in medication prescriptions between subtypes, as well as a large number of unique treatment sequences. These findings are in line with previous studies and illustrate the

FIG. 2 Analysis of treatment sequences prescribed to JIA patients



This figure visualizes sequential lines of treatment prescribed to patients with (**A**) non-systemic JIA ($n = 212$) and (**B**) systemic JIA ($n = 24$) for the first four lines of treatment, regardless of treatment duration. The thickness of the lines reflects the number of patients. Medications are categorized according to their class into systemic steroids, and synthetic or biologic DMARDs (sDMARD and bDMARD, respectively). These bDMARDs are subdivided according to mechanism of action into TNF-α inhibitors, anti-IL-1, anti-IL-6, anti-CD20 and CTLA-4. A switch to the same type of medication (e.g. from sDMARD to sDMARD) implies that a patient received the same type of medication during two consecutive time periods with a period of discontinuation of $\geq$30 days.

strong heterogeneity of JIA disease manifestation and thereby the need for treat-to-target approaches [7, 8, 28].

When considering non-systemic JIA patients, systemic therapy prescriptions are in line with current treatment guidelines, which recommend sDMARDs (MTX) as first-line treatment, and switching to adalimumab and etanercept in case of inadequate response to sDMARDs [29]. Also, 83.3% of systemic JIA patients had anakinra prescribed as first-line treatment. This is in line with current treatment guidelines which recommend anakinra as

Table 3 Annual cumulative proportion of patients starting sDMARDs and bDMARDs

	Enthesitis-related JIA ($n = 31$)	Extended oligoart. JIA ($n = 21$)	Oligoart. persistent JIA, ANA– ($n = 27$)	Oligoart. persistent JIA, ANA+ ($n = 55$)	Polyart. JIA, RF– ($n = 60$)	Polyart. JIA, RF+ ($n = 11$)	PsA ($n = 7$)	Systemic JIA ($n = 24$)	Total ($n = 236$)
Cumulative proportion of patients initiating sDMARD, % (95% CI)									
1 year	90 (72–97)	95 (68–99)	78 (55–89)	76 (62–85)	97 (87–99)	100	86 (12–98)	17 (0–30)	81 (75–85)
2 years	97 (78–100)	100	81 (59–92)	89 (77–95)	98 (88–100)	100	86 (12–98)	21 (3–36)	86 (81–90)
3 years	97 (78–100)	100	85 (63–94)	96 (86–99)	100	100	86 (12–98)	21 (3–36)	89 (84–92)
Cumulative proportion of patients initiating bDMARD, % (95% CI)									
1 year	52 (30–66)	24 (3–40)	30 (10–45)	9 (1–16)	38 (25–49)	73 (28–90)	29 (0–55)	92 (69–98)	38 (31–44)
2 years	52 (30–66)	34 (10–52)	30 (10–45)	15 (5–23)	42 (28–53)	82 (36–95)	29 (0–55)	92 (69–98)	41 (35–47)
3 years	59 (33–74)	48 (18–66)	30 (10–45)	21 (9–32)	44 (30–56)	82 (36–95)	52 (0–81)	92 (69–98)	46 (39–52)
Median estimated time from JIA diagnosis date to the date of first prescription, years (95% CI)									
sDMARD	0.13 (0.03–0.35)	0.01 (0.00–0.38)	0.18 (0.06–0.67)	0.23 (0.10–0.47)	0.03 (0.00–0.07)	0.00 (0.00–∞)	0.00 (0.00–∞)	NE	0.09 (0.07–0.14)
bDMARD	0.96 (0.57–∞)	NE	NE	NE	NE	0.74 (0.27–∞)	2.37 (0.29–∞)	0.01 (0.00–0.04)	NE

NE: not estimated, the median could not be estimated because fewer than 50% of patients had a sDMARD or bDMARD prescribed. ANA–: ANA-negative; ANA+: ANA-positive; bDMARD: biologic DMARD; oligoart.: oligoarticular; polyart.: polyarticular; RF–: RF-negative; RF+: RF-positive; sDMARD: synthetic DMARD.

first-line treatment in systemic JIA, and taper to stop after 3 months in clinical remission [29, 30].

When we exclude patients who continued medication at the end of their follow-up, the medication discontinuation or switching in the remaining patients reveals the real-world medication effectiveness. For example, results indicate that 43% of the MTX prescriptions were discontinued because of remission, i.e. treatment effectiveness. In contrast, 37% and 15% of patients switched to another medicine because of adverse events or ineffectiveness, respectively, indicating treatment failure. When considering a previous study that investigated reasons for MTX monotherapy discontinuation, and when ignoring the 161 patients in whom a bDMARD was added to MTX monotherapy, results indicate that remission was the reason for MTX discontinuation in only 16% of patients, compared with 52% for adverse events, 16% for ineffectiveness and 15% for other reasons [31]. However, this study focussed on the first 2 years of treatment, which likely explains the relatively low proportion of patients in whom MTX was discontinued because of remission.

This study is unique by simultaneously providing insight in treatment types and sequences, as well as in the duration and reasons for medication discontinuation, in a large cohort of Dutch JIA patients. The availability of large datasets on real-world treatment prescriptions is a prerequisite for the use of statistical methods, simulation models and/or machine learning algorithms. These innovative methods have the potential to contribute to optimizing treatment sequences in JIA, which has already been demonstrated in other disease areas including RA [32–34].

This study has limitations to be acknowledged. First, the duration of follow-up varied widely among patients (IQR 2.5–5.8). We mitigated this issue by only including patients with at least 1 year of follow-up and by accounting for censoring through the use of Kaplan–Meier methods. The reported findings are in the context of a median time frame of 4.2 years.

Second, although the use of NSAIDs as well as IA injections are incorporated in current treatment guidelines [29], we could not include these in the analysis. Reasons for not including NSAIDs (e.g. ibuprofen) are (i) because their indication of use is not restricted to JIA, and (ii) because in the Netherlands NSAIDs are available on prescription as well as over-the-counter without prescription. As a consequence, the real-world use of NSAIDs for treating JIA could not be investigated. IA injections were excluded as these represent intermittent medication administrations instead of continuous lines of treatment. However, both NSAIDs and IA injections may have influenced the prescription of sDMARDs, bDMARDs and systemic steroids, potentially affecting the results presented. To illustrate this, of the 59 patients with enthesitis-related JIA in the original database, 28 patients were excluded because not fulfilling the inclusion criteria. Of these, 13 patients were excluded because they did not have a bDMARD,

Table 4 Reasons for medication (dis)continuation depending on drug type (excluding systemic steroids)

	Ineffectiveness, *n* (%)	Adverse event, *n* (%)	Remission, *n* (%)	Patient decision or preference, *n* (%)	Continuing medication at end follow-up, *n* (%)
sDMARDs					
MTX ($n = 316$)					
Oral ($n = 263$)	29 (11.0)	65 (24.7)	82 (31.2)	6 (2.3)	81 (30.8)
Subcutaneous ($n = 53$)	4 (7.5)	15 (28.3)	12 (22.6)	4 (7.5)	18 (34.0)
LEF ($n = 19$)	1 (5.3)	1 (5.3)	6 (31.6)	0 (0.0)	11 (57.9)
SSZ ($n = 9$)	4 (44.4)	1 (11.1)	1 (11.1)	1 (11.1)	2 (22.2)
Other ($n = 10$)	0 (0.0)	2 (20.0)	2 (20.0)	0 (0.0)	6 (60.0)
Total ($n = 354$)	38 (10.7)	84 (23.7)	103 (29.1)	11 (3.1)	118 (33.3)
bDMARDs					
Anti IL1 ($n = 33$)	7 (21.2)	3 (9.1)	17 (51.5)	0 (0.0)	6 (18.2)
Anti IL6 ($n = 17$)	2 (11.8)	1 (5.9)	1 (5.9)	2 (11.8)	11 (64.7)
TNF ($n = 145$)	29 (20.0)	13 (9.0)	35 (24.1)	2 (1.4)	66 (45.5)
Other ($n = 2$)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
Total ($n = 197$)	39 (19.8)	17 (8.6)	53 (26.9)	4 (2.0)	84 (42.6)
Overall ($n = 551$)	77 (14.0)	101 (18.3)	156 (28.3)	15 (2.7)	202 (36.7)

This table shows the reasons for medication (dis)continuation for bDMARDs and sDMARDs for all 551 medication prescriptions among the 236 patients included in the database. bDMARD: biologic DMARD; sDMARD: synthetic DMARD.

sDMARD or systemic steroid prescribed during follow-up, including two patients who received at least one IA injection, and regardless of whether they received NSAIDs.

Third, in the current analysis, switching from (for example) etanercept and adalimumab was not considered a new line of treatment as both are TNF-α inhibitors. Although these may be considered interchangeable when treating joint inflammation, adalimumab is mostly preferred when uveitis or IBD is present [35]. However, only two patients in this analysis switched from etanercept to adalimumab because of uveitis, indicating that this did not substantially affect the results presented.

Although a drawback of single-centre studies, in general, involves the lack of generalizability of study findings, this study was conducted in the largest paediatric rheumatology treatment centre in the Netherlands. In addition, as patients participating in pharmaceutical trials were excluded, results are expected to be highly representative of current practice.

Treatment guidelines and decisions in JIA differ between countries and healthcare systems. To illustrate this, aspects like waiting times prior to treatment initiation are, in contrast to some other countries [36], not an issue in the Netherlands. The results of this study should therefore be interpreted in the context of the Dutch healthcare system. As a consequence, the generalizability of the results presented may be limited to countries or healthcare systems with comparable treatment guidelines, especially with regard to bDMARDs.

Rapid and adequate treatment of JIA decreases time to remission [14, 30, 37]. Although the current study did not consider the impact of treatment on disease activity, the duration of the different treatment lines, the number of treatment switches, as well as reasons for discontinuing medication do provide insight into treatment success rates and are therefore of added value to paediatric rheumatologists.

In addition, bDMARD prescription decisions are not only affected by their expected impact on achieving remission, but also by their costs. Although previous studies have investigated the impact of JIA treatment, including bDMARDs, on costs [17–19, 38, 39], the health economic impact of personalized JIA treatment is unknown. Therefore, future research should balance these medication costs against their impact on reducing disease activity, healthcare consumption, and wider impacts to patients, parents and society, which is currently investigated in the Canada Netherlands Personalized Medicine Network in Childhood Arthritis and Rheumatic Disease (i.e. the UCAN CAN-DU study) [40].

The range of medicines prescribed in JIA, the substantial variation in medication prescriptions between JIA subtypes, the large number of patients receiving two or more treatment lines (either in monotherapy or combination), as well as the large number of unique treatment sequences observed, reveals the complexity of pharmacological treatment in JIA. The prescription of bDMARDs and sDMARDs are in line with Dutch clinical guidelines. The real-world data reveal that remission (i.e. treatment effectiveness) was the most common reason for discontinuing sDMARDs and bDMARDs. These insights into real-world medication prescriptions are an important first step for developing simulation models or machine learning algorithms for optimizing JIA treatment sequences. In turn, integrating these prescription patterns with data on health outcomes enables one to decide in which patients the additional costs of first-line bDMARD treatment would be offset against their benefits in terms of early disease remission, and its

accompanying long-term health economic benefits to patients, parents and society.

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Data availability statement

The data that support the findings of this study are available upon reasonable request and by contacting the corresponding author, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with the permission of J.F.S.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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