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Real world prescription patterns and costs of drug treatment in juvenile idiopathic arthritis in the Netherlands

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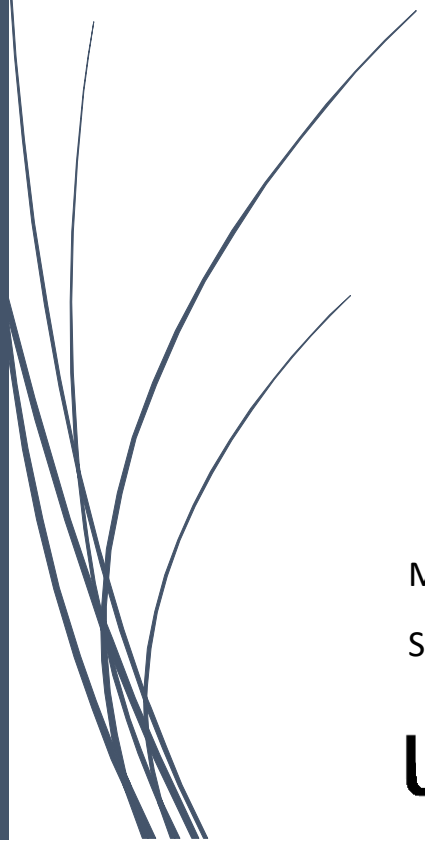

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Abstract

Objective

Juvenile idiopathic arthritis (JIA) represents seven forms of chronic arthritis in children. Inadequately treated, it may result in lifelong disability. Treatment of JIA usually involves methotrexate (MTX) as 1st line therapy, and (more costly) biological disease-modifying anti-rheumatic drugs (DMARDs) as second-line treatment. However, in systemic JIA, biological DMARDs are used as 1st line treatment. To achieve adequate disease control, many different combinations and sequences of medication may be necessary. This study aims to describe different lines of treatment for JIA patients and to quantify the accompanying impact on drug costs.

Methods

A cohort of 884 JIA patients (0-18 years), treated in the Wilhelmina Children's Hospital (the Netherlands), between 1 April 2011 and 9 April 2019 was analysed. Data on the type, frequency and duration of medication prescribed to these patients were retrieved from the hospital administrative system. Prescribed doses and accompanying cost prices were retrieved from the Dutch paediatric formulary and the Dutch Pharmacotherapeutic Compass, to calculate the average annual costs of medication per patient.

Results

Twenty different (combinations of) drugs were used as 1st line treatment, compared with 35 as 2nd line treatment. Oral MTX was the most commonly prescribed 1st line treatment (56.7% of patients), compared with 39.1% in second-line (including combination therapies). On average, patients receive 2.3 lines of treatment during an average 4.4 year follow-up period. The average annual costs/patient range from €93 for undifferentiated JIA to €8,676 for systemic JIA. This difference was mainly attributable to the high costs of biologics (84.7% of total drug costs). Canakinumab was only used among systemic JIA patients and by far the most expensive, costing on average €60,156/patient/year over the entire follow-up period.

Conclusion

Pharmacological treatment of JIA is complex and warrants an individualized approach. Systemic JIA represents the subgroup with the highest medication costs, which is attributable to 1) the use of biological DMARDs in the 1st line, 2) the use of canakinumab, which is restricted to systemic JIA patients.

Introduction

Juvenile idiopathic arthritis (JIA) is a broad term describing arthritides of unknown causes which manifest itself before the age of sixteen and persists for more than six weeks [1]. The prevalence of JIA is approximately 1 per 1,000 children [1]. Symptoms of JIA include pain and impaired musculoskeletal function and these symptoms may persist into adulthood, potentially resulting in a reduced ability to work [2]. Although JIA cannot be cured, treatment is crucial to achieve control of the disease, thereby preventing or minimizing long-term consequences. A major part of this treatment consists of drug treatment and many different drugs are available [3].

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and/or moderate or high-dose systemic corticosteroid therapy used to be the treatment of choice to treat JIA [3]. In addition, intra-articular injections (i.e. depots) with steroids, for example triamcinolone hexacetonide, are often provided in the treatment of JIA [3].

When treatment with only NSAIDs, systemic corticosteroids and/or depots is not sufficient to control the disease, disease-modifying anti-rheumatic drugs (DMARDs) are prescribed to treat JIA [4]. There are two forms of DMARDs, namely the non-biological and biological DMARDs. Methotrexate (MTX) is the non-biological DMARD of first choice because of its effectiveness and acceptable toxic effects [3]. However, in some JIA patients, treatment with non-biological DMARDs is not sufficient to achieve control of the disease. In those cases, treatment with a biological DMARD is recommended [3]. For

patients with systemic JIA, the most severe subtype of JIA, treatment starts with a biological DMARD [1].

Although the introduction of biological DMARDs improved the treatment for JIA patients, this also led to an increase in costs [3]. In addition, partly due to the availability of biologicals, determining the most suitable drug for each individual patient remains a challenge to physicians. Consequently, many JIA patients still undergo multiple switches in drug treatment before clinical inactive disease/remission is achieved, resulting in unfavourable patient outcomes and high costs [3].

The total healthcare related costs are rising as a result of more complex treatments, more expensive medication and an aging population. The question which rises from this problem is how to spent the total budget? The costs for treating JIA patients are also rising due to the introduction of biological DMARDs for example, however, the available budget for treating JIA patients stays the same.
The costs for drug treatment of JIA patients are high, however, the exact costs on patient level are unknown. Current literature does not describe the costs per subtype of JIA or per biological DMARD on patient level. The aim of this research is to show possible treatment pathways for drug treatment of JIA patients and to analyse the costs of drug treatment for JIA patients and create a more complete overview of these costs. This research is a new and extensive analysis of existing data. This analysis is unique, because the focus is on all subtypes of JIA and the costs, over a long time horizon with a relative large research population.
Two research questions have been defined:

1) How complex is drug treatment for JIA patients? This questions is answered with some sub questions:
   Are there any patient characteristics based on age, gender, residence and JIA subtype which explain successful 1st line treatment with MTX? What is the probability of successful 1st line treatment/1st line MTX treatment? How many lines of treatment with biological and/or non-biological DMARDs and/or steroids are used on average? And which combinations of medication with biological and/or non-biological DMARDs and/or steroids are often used? 1st line treatment is defined as the first drug(s) prescribed after diagnosis.
2) What are the average costs of medication use per patient per year for each subtype of JIA and per biological DMARD?

Methods

The database used consists of patients participating in the PharmaChild registry and treated in the Wilhelmina Children's hospital in the Netherlands between 1 April 2011 and 9 April 2019. Patients who were already 18 at 1 April 2011 and patients who were referred to the Wilhelmina Children's Hospital specifically for a second opinion, or only for their participation in a study (e.g. the Canakinumab study), were excluded from the analysis. Patients who only participated in the Canakinumab study in the Wilhelmina Children's Hospital were excluded, because of the high costs for canakinumab and because these patients are not treated in the Wilhelmina Children's Hospital besides the study and therefore these patients are not considered real patients of the Wilhelmina Children's Hospital. Besides medication use, the data contained information about the year of birth, gender, diagnosis, diagnosis date, Body Mass Index (BMI) and zip code. All patient identification data was coded and for every patient an unique PseudoID was used.
According to the ILAR classification [5], there are 7 subtypes of JIA. The heterogeneous oligoarticular and polyarticular JIA subgroups were subdivided respectively in three and two subtypes resulting in a total of 10 subgroups:

- Enthesitis related JIA
- Extended oligoarticular JIA
- JIA undifferentiated
- JIA uveitis

- Oligoarticular persistent JIA – ANA negative
- Oligoarticular persistent JIA – ANA positive
- Polyarticular JIA RF negative
- Polyarticular JIA RF positive
- Psoriatic arthritis
- Systemic JIA / Still

The database used concerned a printout of (coded) patient files from the Wilhelmina Children's Hospital and contained two files about medication use. These files were the 1) the DMARD file, in which all DMARDs (biological and non-biological) and steroids (including intra-articular corticosteroid depots) were registered manually by the treating physician and 2) the pharmacy registry, a printout of the hospital pharmacy specifying all medication prescribed to individual patients in the database. After cross-checking, the DMARD file was found to be better suitable for the purpose of the current analysis, as this DMARD file better captures whether a patient actually took the medication, whereas the pharmacy registry only captures whether or not medication was prescribed to a patient. Therefore, the DMARD file was used to calculate the costs for the DMARDs (biological and non-biological), steroids and depots. For the remaining medication, the pharmacy registry was used.

Patient characteristics
The characteristics of all patients with a current diagnosis of JIA were determined, including age at diagnosis, mean length of follow-up, gender, BMI category (i.e. underweight, normal, overweight and obese) and JIA subtype.

Sequence of medication use for DMARDs and steroids
In order to capture 1st line treatment, only patients with a diagnosis date at 01-04-2011 or later were used for these particular analyses. The 1st line treatment was defined as the first drug prescribed after JIA diagnosis. When this drug was not sufficient to achieve control of the disease or the side effects of a certain drug were intolerable, a switch in prescribed drug(s) was made, or a second drug was added. This new drug, or the new combination of drugs, is referred to as 2nd line treatment.
The sequence of medication use was first used to determine any patient characteristics which may explain an increased probability of successful 1st line MTX treatment. Successful 1st line treatment means there is no switch in prescribed drug(s) after the drugs prescribed as 1st line treatment. To investigate this, two subgroups were created: 1) patients who received MTX as 1st line treatment and 2) patients who received MTX as 1st line treatment but in whom this was not successful. The characteristics which were determined are the same as the characteristics mentioned in the paragraph about patient characteristics.
The sequence of medication was also used to determine the probability of successful 1st line treatment/successful 1st line MTX treatment. These probabilities were determined for only systemic JIA patients and for the other nine subtypes of JIA together.
These analyses are explained in more detail in Appendix A.
Furthermore, the sequence of medication use was also used to determine the average amount of lines of treatment with a biological and/or non-biological DMARD and/or steroid per patient. Finally, the sequence of medication use was used to identify often prescribed combinations of medication with biological and/or non-biological DMARDs and/or steroids.

Furthermore, sunburst charts for the 1st and 2nd line treatment were designed to visualize the switches in prescribed medication. Separate sunburst charts were designed for the systemic JIA subtype and for all other subtypes of JIA. In these sunburst charts, the 1st line treatment is visualized on the inner ring, whereas the 2nd line treatment is visualized on the outer ring. The size of a part represents the proportion of patients who received a particular type (or combination) of drug(s).

Medication use

All biological and non-biological DMARDs and steroids from the DMARD file were used in this analysis.

In the pharmacy registry, there were almost 2000 different kinds of medication and/or different doses and/or different forms of administration for a certain drug. Only the drugs which were prescribed more than 10 times and were no biological or non-biological DMARD or steroid, were used in this analysis. The remaining drugs in the pharmacy registry were categorized according to type of drugs and send to a paediatric rheumatologist for review. The categories which were created are:

1. Eye drops.
2. NSAIDs and other painkillers.
3. Antibiotics.
4. Immune suppressants.
5. Cream and shampoos.
6. Sleep medication, anti-depressants and anti-epileptics.
7. Vitamins.
8. Other medication, like medication for heart diseases, birth control and anaesthesia.

The categories 1 till 4 were considered relevant for calculating the costs of a JIA patient. Only eye drops, NSAIDs and other painkillers and immune suppressants are prescribed as part of JIA treatment. As the use of immune suppressants (which is required for JIA) is associated with an increased risk of infections, antibiotics are used to treat these infections. The other four categories of medication are not used in this research.

The start date of the analysis was 1 April 2011 (for patients diagnosed with JIA before this date), for patients diagnosed after 1 April 2011, the diagnosis date was set as starting point for the current analysis. The end date of the analysis was 9 April 2019 (for patients who were not 18 at that date), for patients who turned 18 before 9 April 2019, the date on which the patient turned 18 was set as end point for the current analysis. The number of days between the start and end of the analysis was defined as the length of follow-up.

In order to quantify the amount of medication used, two steps were performed:

First, the duration of medication prescriptions (in days) were determined for each type of medication and for each patient.

For all DMARDs (biological and non-biological), steroids and depots, start and stop dates were entered manually by the treating paediatric rheumatologist. All start dates occurring before 1 April 2011 (i.e. the start date of the current analysis), were set to 1 April 2011. Similarly, all medication continuing after the end date of the analysis were corrected to 9 April 2019 (the end date of the analysis). In case the exact start or stop day was missing, this date was manually set at the first day of the month.

For all remaining medication (i.e. eye drops, NSAIDs, antibiotics and immune suppressants), the duration of medication prescriptions (in days) was determined based on the pharmacy registry of the WKZ. In the pharmacy registry, some start and stop dates were missing or incorrect. Incorrect dates were for example an end date before the start date. When the start or stop day and month were unknown, the start or stop date was set at 1 January of that year. When only the start or stop day was unknown, the start or stop date was set at the first of the month. The method to correct all missing and incorrect start and stop dates is explained in detail in Appendix B.

Second, the dose was determined for each drug.

For all biological and non-biological DMARDs and steroids, the required dose was retrieved from the Dutch paediatric formulary [6].

For all remaining medication, the required doses were retrieved from the pharmacy registry. The average dose over all patients for a certain drug was used in the analysis.

Medication costs

The costs for all biological and non-biological DMARDs, steroids and the medication from the four categories of medication from the pharmacy registry were retrieved from the Dutch Pharmacotherapeutic Compass [7]. Especially for the drugs in the four categories from the pharmacy registry, there were different modes of administration (i.e. capsules, nose/eye drops, concentrations for injections/oral intake and salves). The method to calculate the average costs per drug per day is explained in detail in Appendix C.

For certain DMARDs and steroids, multiple cost prices were displayed in the Dutch Pharmacotherapeutic Compass [7], as well as multiple administration forms and doses. The average of all these costs was used in the calculations. The costs per day were determined by dividing the average costs by the amount of days between two treatments found in the Dutch paediatric formulary [6].

Multiplying the costs per day with the amount of days that a patient used a certain drug gave the total costs for that drug. The costs per patient per year were calculated by dividing the total costs by the length of follow-up for that patient.

The average costs per patient per year per JIA subtype for all subgroups of medication (i.e. biological DMARDs, non-biological DMARDs, steroids, depots and medication from the four categories of medication from the pharmacy registry) were compared. Expensive medication or expensive kinds of medication were identified by comparing the ratio between the amount of days used and the length of follow-up with the costs per patient per year. The average costs per patient per year for each biological DMARD were determined and compared.

All costs were expressed in 2019 Euros. Discounting was not applied, because the costs from all previous years were equally important in this retrospective cost analysis. Furthermore, there were no large fluctuations in the prices for biological DMARDs and the biosimilars were not available yet for paediatrics.

Analysis

All analyses were performed in Microsoft Excel 2016 and R studio version 3.5.1 (2018-07-02) [8]. Figures were created in Microsoft Excel 2016 and percentages for all characteristics were determined with R studio.

Results

Flowchart exclusion criteria

There were two exclusion criteria for this research: 1) patients who were already 18 years old at 01-04-2011 and 2) patients who were referred to the Wilhelmina Children's Hospital for a second opinion or only to participate in the Canakinumab study. A flowchart for these exclusion criteria is displayed in Figure 1.

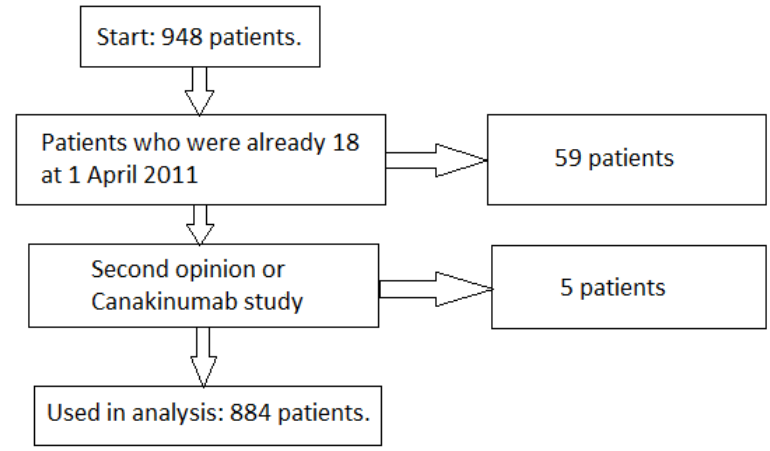

Figure 1: Flowchart exclusion criteria

Patient characteristics

From the database, the most important patient characteristics are determined. These characteristics are displayed in Table 1.

Table 1: Patient characteristics

Total number of patients	**884 patients**
Mean age at diagnosis in years (SD)	8.8 (4.9)
Mean follow up period in years (SD)	4.4 (2.4)
Gender (%)	
- Female	561 (63.5%)
- Male	323 (36.5%)
BMI category (%)	
- Underweight	150 (17.0%)
- Normal	592 (67.0%)
- Overweight	99 (11.2%)
- Obese	35 (4.0%)
- Unknown (not measured)	8 (0.9%)
Region (%)	
- Province of Utrecht	254 (28.38%)
- Other provinces	641 (71.62%)
Diagnosis (%):	
- Oligoarticular persistent JIA – ANA positive	168 (19.0%)
- Polyarticular JIA RF negative	167 (18.9%)
- Oligoarticular persistent JIA – ANA negative	164 (18.6%)
- Systemic JIA / Still	87 (9.8%)
- Extended oligoarticular JIA	84 (9.5%)
- Enthesitis related JIA	75 (8.5%)
- JIA uveitis	57 (6.4%)
- Polyarticular JIA RF positive	38 (4.3%)
- Psoriatic arthritis	34 (3.8%)
- JIA undifferentiated	10 (1.1%)

Sequence of medication use for DMARDs and steroids

First, the patient characteristics which may explain an increased probability of successful 1st line MTX treatment are determined. The characteristics are determined for all patients who received biological and/or non-biological DMARDs and/or steroids and for the two subgroups mentioned in the methods section: patients who received MTX in the 1st line and patients in which MTX 1st line treatment was not successful.

The characteristics for these three groups are displayed in Table 2.

Table 2: Characteristics all patients who received biological and/or non-biological DMARDs and/or steroids, patients with MTX in 1st line and patients with failure MTX treatment in 1st line

	All patients who received DMARDs and/or steroids	**MTX in 1st line (subgroup 1)**	**Failure MTX treatment in 1st line (subgroup 2)**
Total number of patients	**473 patients**	**325 patients**	**114 patients**
Mean age at diagnosis in years (SD)	8.7 (5.0)	8.5 (5.0)	9.2 (4.9)
Mean follow up period in years (SD)	4.6 (2.4)	4.7 (2.5)	4.6 (2.4)
Gender (%)			
- Female	325 (68.7%)	230 (70.8%)	80 (70.2%)
- Male	148 (31.3%)	95 (29.2%)	34 (29.8%)
BMI category (%)			
- Underweight	67 (14.2%)	50 (15.4%)	20 (17.5%)
- Normal	326 (68.9%)	221 (68.0%)	69 (60.5%)
- Overweight	58 (12.3%)	41 (12.6%)	16 (14.0%)
- Obese	22 (4.7%)	13 (4.0%)	9 (7.9%)
Region (%)			
- Province of Utrecht	143 (30.2%)	106 (32.6%)	41 (36.0%)
- Other provinces	330 (69.8%)	219 (67.4%)	73 (64.0%)

Diagnosis (%)			
- Polyarticular JIA RF negative	111 (23.5%)	81 (24.9%)	36 (31.6%)
- Oligoarticular persistent JIA – ANA positive	98 (20.7%)	86 (26.5%)	26 (22.8%)
- Extended oligoarticular JIA	62 (13.1%)	42 (12.9%)	10 (8.8%)
- Oligoarticular persistent JIA – ANA negative	53 (11.2%)	43 (13.2%)	12 (10.5%)
- Systemic JIA / Still	47 (9.9%)	7 (2.2%)	3 (2.6%)
- Enthesitis related JIA	45 (9.5%)	28 (8.6%)	12 (10.5%)
- Polyarticular JIA RF positive	31 (6.6%)	19 (5.8%)	8 (7.0%)
- Psoriatic arthritis	16 (3.4%)	13 (4.0%)	6 (5.3%)
- JIA uveitis	8 (1.7%)	4 (1.2%)	1 (0.9%)
- JIA undifferentiated	2 (0.4%)	2 (0.6%)	0 (0%)

Second, the probability of successful 1st line treatment is determined for 1) patients with systemic JIA and 2) for the other nine subtypes of JIA together.
From the 47 systemic JIA patients (group 1), 28 had no switch after the 1st prescribed drug(s). This gives a probability of 60.0% for successful 1st line treatment for systemic JIA patients.
From the 426 patients with another subtype of JIA than systemic JIA (group 2), 193 had no switch after the 1st prescribed drug(s). This gives a probability of 45.3% for successful 1st line treatment in patients with another subtype than systemic JIA.
Furthermore, the probability of successful 1st line MTX treatment is determined for all subtypes of JIA together, except systemic JIA. From the 426 patients with another subtype of JIA than systemic JIA, 318 received MTX in the 1st line treatment. From those 318 patients, 207 also had MTX in the 2nd line treatment. This gives a probability of 65.1% for successful 1st line MTX treatment in patients with another subtype than systemic JIA.

Third, the average amount of lines of treatment with a biological and/or non-biological DMARD and/or steroid per patient is determined. The average amount of lines of treatment for systemic JIA patients is 2.2 and for the other nine subtypes of JIA together 2.3.

Finally, frequently prescribed combinations of medication are identified. The most frequently prescribed combination of medication is oral MTX with adalimumab (n=11), followed by the combination of leflunomide with oral MTX (n=5).

For the systemic JIA subtype, 1st line treatment consists of a biological DMARD [1]. For all other subtypes of JIA, 1st line treatment consists of a non-biological DMARD or steroid. Sunburst charts for the 1st and 2nd line treatment are designed to verify this statement. Figure 2 displays the sunburst chart for all subtypes of JIA, except systemic JIA. Figure 3 displays the sunburst for only the systemic JIA subtype.

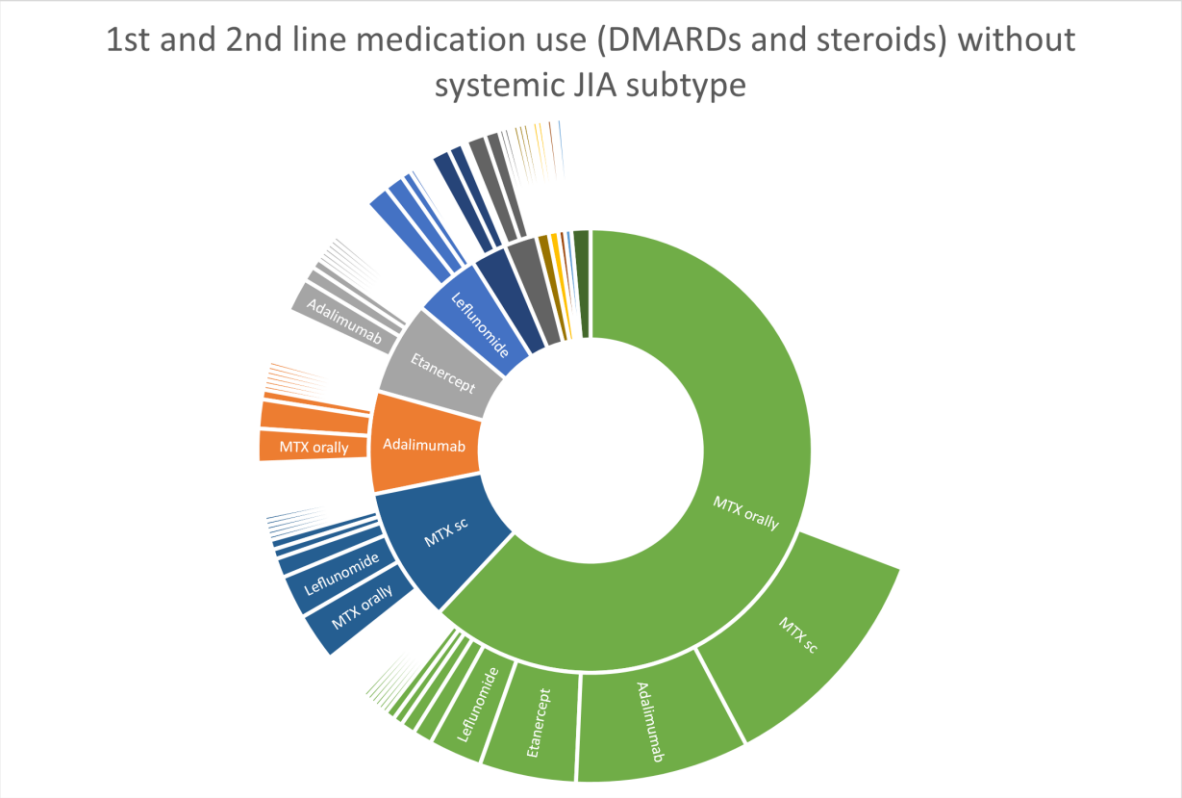

Figure 2: Sunburst chart of 1st and 2nd line medication use for DMARDs and steroids without systemic JIA subtype, including combination therapy

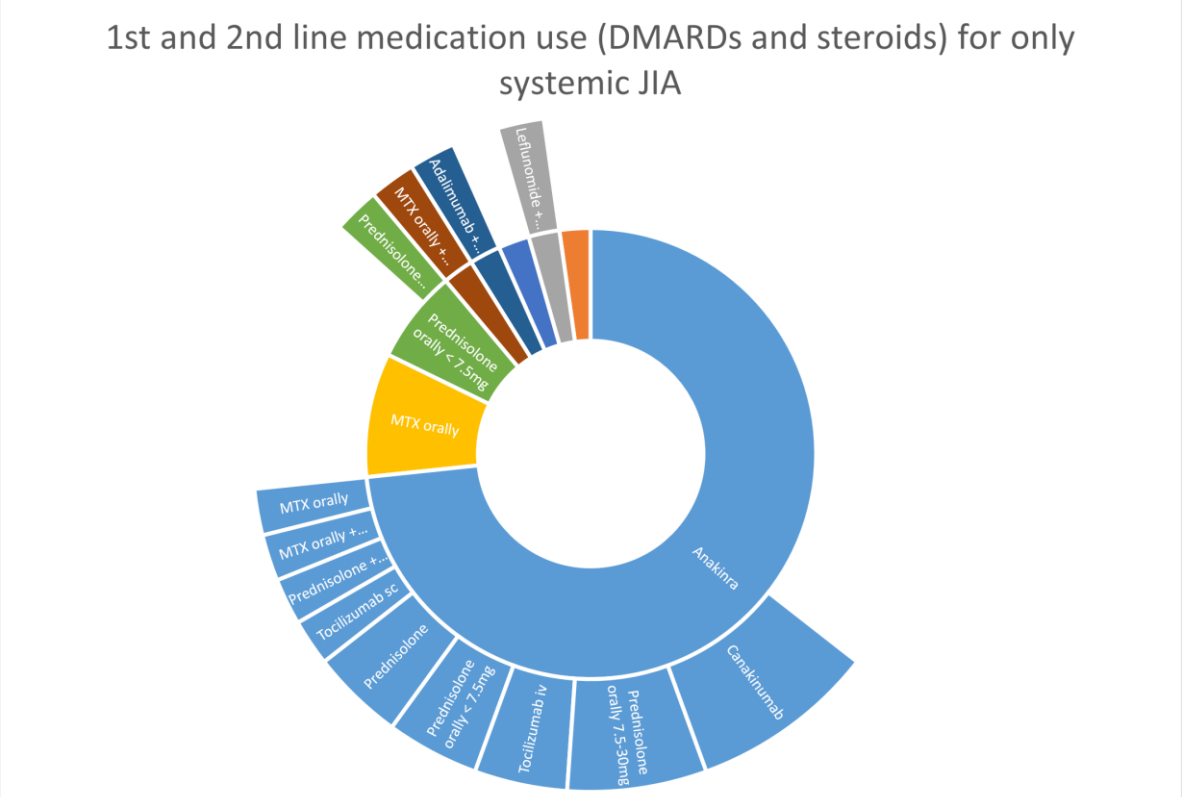

Figure 3: Sunburst chart of 1st and 2nd line medication use for DMARDs and steroids of only the systemic JIA subtype, including combination therapy

All drugs shown in the two sunburst diagrams can be categorized in subgroups (i.e. biological DMARDs, non-biological DMARDs and steroids). A list of all DMARDs and steroids and the subgroup they belong to can be found in Table 6 in Appendix D. A sunburst with these groups of medication is shown in Figure 7 in Appendix D.

The results indicate that 20 different (combinations of) pharmacological treatment were used as 1st line treatment, and 35 (combinations of) pharmacological treatment as 2nd line in the entire research population. On average, patients receive 2.3 lines of treatment during an average 4.4 year follow-up period. MTX orally was the most commonly prescribed 1st line treatment (56.7% of patients), compared with 39.1% in the 2nd line.
For systemic JIA patients, 76.6% received a biological DMARD in the 1st line.

Medication costs
The costs per patient per year for the biological and non-biological DMARDs and steroids and the medication from the four categories of medication from the pharmacy registry together are determined and shown in Table 3. Table 3 shows the mean costs, IQR 25% and IQR 75% for each subtype of JIA.

Table 3: Mean costs, IQR 25% and IQR 75% per patient per year of the biological and non-biological DMARDs and steroids and the medication from the four categories of medication from the pharmacy registry together per subtype of JIA

Diagnosis	Number of patients	Mean costs	IQR 25%	IQR 75%
JIA undifferentiated	10	€ 93	€ 0	€ 104
Oligoarticular persistent JIA - ANA negative	164	€ 996	€ 0	€ 1,448
JIA uveitis	57	€ 2,159	€ 0	€ 6,762
Psoriatic arthritis	34	€ 2,438	€ 0	€ 9,427
Oligoarticular persistent JIA - ANA positive	168	€ 2,821	€ 2	€ 5,073
Polyarticular JIA RF negative	167	€ 3,026	€ 0	€ 10,472
Enthesitis related JIA	75	€ 3,226	€ 0	€ 12,679
Extended oligoarticular JIA	84	€ 3,326	€ 1	€ 9,948
Polyarticular JIA RF positive	38	€ 4,934	€ 8	€ 11,925
Systemic JIA / Still	87	€ 8,676	€ 0	€ 12,106
Total	884			
Mean		€ 3,169		

Table 3 shows the average annual total costs per patient for each subtype of JIA. For the total costs, it is determined which part is attributable to biological DMARDs (shown in blue), and which part is attributable to any other type of medication included in the current analysis (shown in orange). These results are shown in Figure 4.

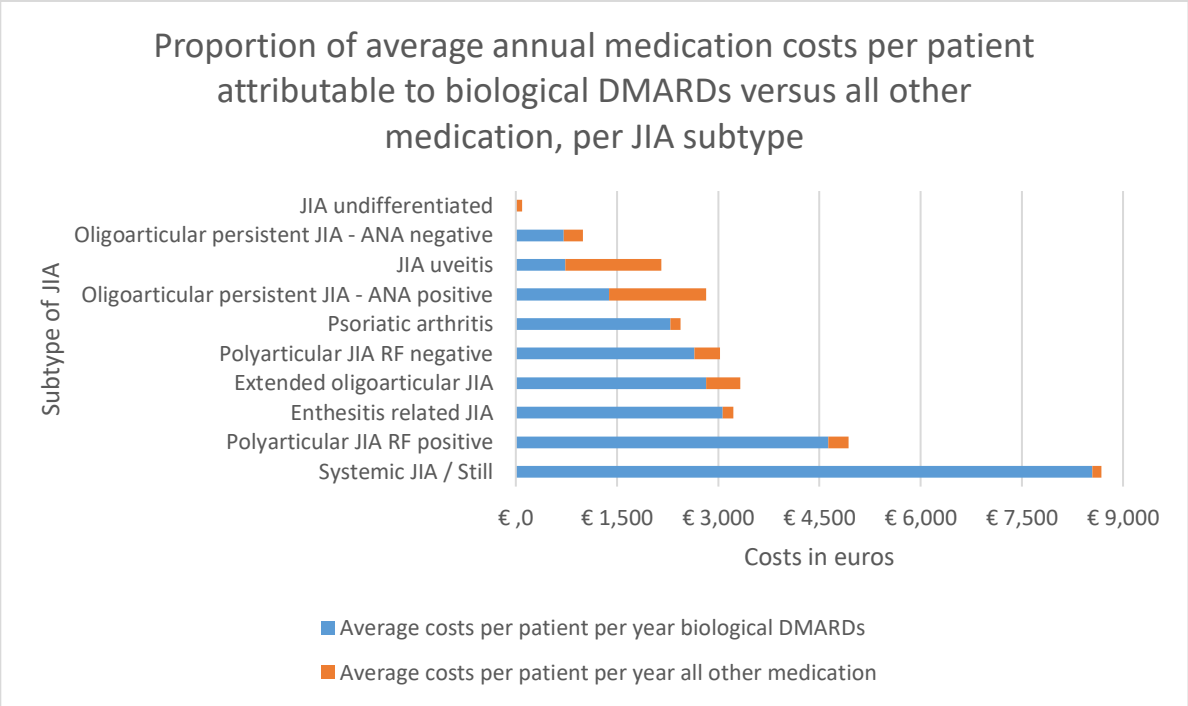

Figure 4: Proportion of average annual medication costs per patient attributable to biological DMARDs versus all other medication (non-biological DMARDs, steroids, depots and the medication from the four categories of medication from the pharmacy registry), per subtype of JIA

Figure 4 shows that especially the biological DMARDs contribute to the majority of costs of medication use in almost all JIA subtypes (84.7% of total drug costs), except among patients with uveitis and oligoarticular persistent JIA – ANA positive, since for these subtypes the orange part is larger compared to the blue part in Figure 4. For JIA uveitis, the large orange part can be explained by the use of eye drops.
The average costs per patient per year for biological DMARDs, non-biological DMARDs, steroids, depots and the medication from the four categories of medication from the pharmacy registry are determined. These costs are displayed in Table 4.

Table 4: Costs per group of medication. Costs are the average costs per patient per year for the JIA subtypes.

Diagnosis	Biological DMARDs	Non-biological DMARDs	Steroids	Depots	Pharmacy registry
JIA undifferentiated	€ 0	€ 6	€ 0	€ 26	€ 61
Oligoarticular persistent JIA - ANA negative	€ 711	€ 67	€ 0	€ 21	€ 197
JIA uveitis	€ 731	€ 129	€ 3	€ 1	€ 1,296
Oligoarticular persistent JIA - ANA positive	€ 1,384	€ 90	€ 13	€ 29	€ 1,306
Psoriatic arthritis	€ 2,295	€ 67	€ 1	€ 13	€ 62
Polyarticular JIA RF negative	€ 2,648	€ 143	€ 10	€ 11	€ 214
Extended oligoarticular JIA	€ 2,818	€ 197	€ 13	€ 20	€ 277
Enthesitis related JIA	€ 3,064	€ 70	€ 0	€ 5	€ 88
Polyarticular JIA RF positive	€ 4,634	€ 211	€ 38	€ 13	€ 39
Systemic JIA / Still	€ 8,546	€ 26	€ 41	€ 2	€ 61

Columns 2 till 5 of Table 4 are visualized in Figure 8 in Appendix E. Figure 8 shows the part of the average costs per patient per year for the four groups of medication mentioned in columns 2 till 5 from Table 4.

Besides distinguishing medication costs per patient according to the subtype of JIA, the costs can also be determined per type of medication (i.e. biological DMARDs vs. non-biological DMARDs, as well as the costs of the different types of non-biological DMARDs). The average amount of days used per year is approximately 81 for non-biological DMARDs and 85 for biological DMARDs. This average amount of days used per year is defined as the ratio between the days that a certain drug is prescribed and the length of follow-up in years. By multiplying this ratio with 365 days, the average amount of days used is calculated. The costs per patient per year for non-biological DMARDs are approximately €100 and for biological DMARDs €2,500.

Within the non-biological DMARDs, MTX is prescribed the most frequently (56.7% of all patients receive MTX orally in the 1st line). Besides MTX orally, MTX subcutaneously (sc) is another form of administration. The average amount of days used and the average costs per patient per year for non-biological DMARDs are displayed in Figure 5 and 6 respectively.

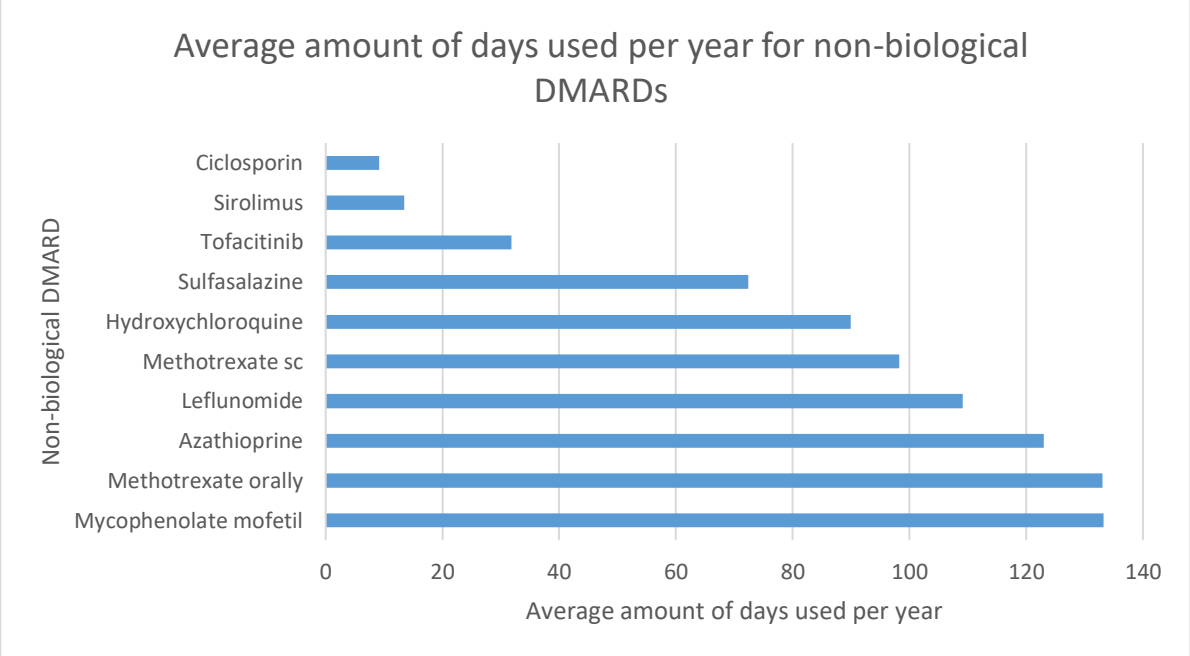

Figure 5: Average amount of days used per year for non-biological DMARDs

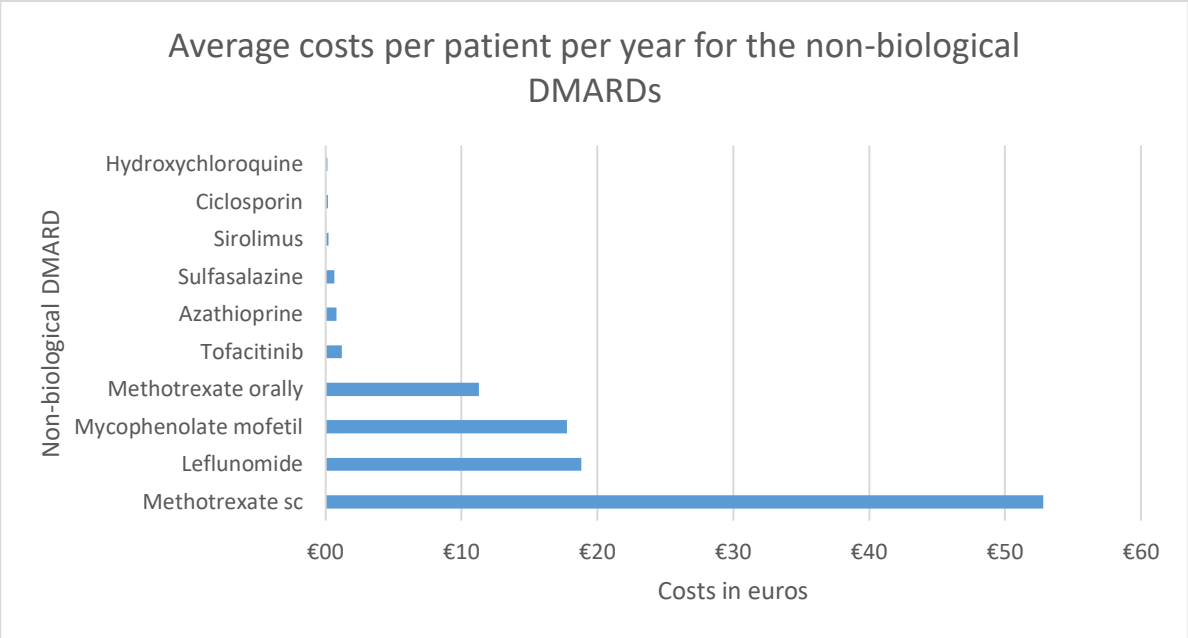

Figure 6: Average costs per patient per year for non-biological DMARDs

In addition, the costs per patient per year between the different biological DMARDs were compared. In Table 5, the number of patients, the average costs per patient per year, the average total costs per patient (over the entire follow-up period), the average length of follow-up in years and the total costs per year for all patients together are displayed. From Table 5 it can be seen that canakinumab is the most expensive drug by looking at the average costs per patient per year. By looking at the total costs per year for all patients together, adalimumab is the most expensive drug. This is due to the high number of patients who receive adalimumab.

Table 5: Number of patients, average costs per patient per year, average total costs per patient, average length of follow-up in years and total costs per year for all patients together, per biological DMARD.

Biological DMARD (group)	Number of patients	Average costs per patient per year	Average total costs per patient	Average length of follow-up in years	Total costs per year for all patients together
Canakinumab (anti-IL-1)	9	€ 60,156	€ 288,569	5.0	€ 541,406
Tocilizumab iv (anti-IL-6)	20	€ 7,117	€ 33,968	5.2	€ 142,339
Adalimumab (TNF-alpha-inhibitor)	154	€ 6,491	€ 27,317	4.9	€ 999,597
Etanercept (TNF-alpha-inhibitor)	110	€ 3,513	€ 17,833	5.4	€ 386,375
Anakinra (anti-IL-1)	42	€ 3,068	€ 9,869	4.1	€ 128,843
Golimumab (TNF-alpha-inhibitor)	16	€ 2,961	€ 12,246	5.0	€ 47,378
Ustekinumab (anti-IL-23)	2	€ 2,534	€ 20,330	8.0	€ 5,069
Tocilizumab sc (anti-IL-6)	17	€ 1,821	€ 7,181	4.9	€ 30,961
Abatacept iv (CTLA-4)	6	€ 1,090	€ 5,355	6.4	€ 6,539
Infliximab (TNF-alpha-inhibitor)	8	€ 858	€ 5,013	6.4	€ 6,866
Abatacept sc (CTLA-4)	2	€ 734	€ 1,568	2.4	€ 1,468
Rituximab (anti-CD20)	1	€ 181	€ 1,290	7.1	€ 181
Sarilumab (anti-IL-6)	1	€ 134	€ 932	6.9	€ 134

Discussion

This research shows that many different pharmaceutical treatment strategies are currently applied in JIA patients, indicating that the treatment process is complex.
The overall probability of successful 1st line treatment is 46.7% (i.e. for all subtypes of JIA together). When only considering systemic JIA, the probability of successful 1st line treatment is 60.0%. For the other nine subtypes together, this is 45.3%. When only considering the probability of successful 1st line treatment with MTX (within this subgroup), this probability is 65.1%.
On average, JIA patients received 2.3 lines of treatment during the follow-up period.
Biological DMARDs are by far the most expensive drugs prescribed among JIA patients. For patients with systemic JIA, biological DMARDs are often used as 1st line treatment and therefore the costs per patient per year are the highest for the systemic subtype. From all biological DMARDs, canakinumab is the most expensive.

Sequence of medication use for DMARDs and steroids

The sequence of medication use is first used to determine any patient characteristics which may explain an increased probability of successful 1st line MTX treatment. Results indicate that the percentage of patients with systemic JIA who receive MTX as 1st line treatment is only 2.2%. In contrast, the percentage of patients with systemic JIA who received any DMARDs and/or steroids is 9.9%. These numbers can be found in Table 2. This supports the statement that patients with systemic JIA are often treated with biological DMARDs in the 1st line (for 76.6% of all patients with systemic JIA).
When comparing the characteristics in Table 2, there is one number which is remarkable. This number is the percentage for the subtype polyarticular JIA RF negative who fail 1st line MTX treatment. For polyarticular JIA RF negative, the percentage failure of 1st line MTX treatment is 31.6% and therefore the highest of all JIA subtypes. This indicates that 1st line MTX treatment is often not successful in patients with RF negative polyarticular JIA. This could be explained by the relative large number of joints that are affected in patients with polyarticular JIA RF negative and that therefore MTX is not sufficient to achieve control of the disease. However, in that case the same should hold for patients with polyarticular JIA RF positive, which is not the case. The fact that rheumatic factor (RF) is negative could be another explanation for the fact that patients with polyarticular JIA RF negative do not respond sufficiently at MTX. To verify this statement, further research is necessary.

Second, the sequence of medication use is used to determine the probabilities of successful 1st line treatment (for only systemic JIA and for the nine remaining subtypes) and of successful 1st line MTX treatment (for nine subtypes of JIA, systemic JIA excluded).
The probability of successful 1st line MTX treatment is only determined for nine subtypes of JIA together, systemic JIA excluded, because for systemic JIA 1st line treatment consists of a biological DMARD and MTX is a non-biological DMARD.
The probability of successful 1st line MTX treatment for the nine subtypes of JIA together (65.1%) is quite high and this indicates that 1st line MTX treatment is successful in most of the cases. The probability of successful 1st line treatment is higher for systemic JIA (60.0%) compared to the other nine subtypes of JIA together (45.3%). This can be explained by the fact that biological DMARDs are used as 1st line treatment for systemic JIA patients [1]. The probability of successful 1st line MTX treatment is higher than the probability of successful 1st line treatment for the nine subtypes of JIA (65.1% versus 45.3%). This indicates that 1st line MTX treatment is more effective compared to other 1st line treatments, which corresponds to the findings from literature [3].

Third, the sequence of medication use is used to determine the average amount of lines of treatment. The average amount of lines of treatment supports the statement that drug treatment for JIA patients is complex and that switches in prescribed drug(s) are often necessary. Systemic JIA is treated with biological DMARDs in the 1st line [1]. For other subtypes of JIA it is not clear which

treatment strategy is the most suitable. Therefore it was expected that for the other subtypes of JIA the average amount of lines of treatment was much higher compared to systemic JIA. This research shows this is not the case (2.2 for systemic JIA and 2.3 for the other subtypes of JIA).

Finally, the sequence of medication use is used to identify often prescribed combinations of medication. With regard to the use of oral MTX, adalimumab and leflunomide are prescribed the most in combination with oral MTX. In both combinations, MTX orally is used. This supports the statement that treatment with MTX orally is often used because of its effectiveness and acceptable toxic effects [3].

The sunburst charts in Figure 2 and Figure 3 show that for systemic JIA anakinra is prescribed the most in the 1st line and for the other subtypes of JIA, the non-biological DMARD MTX orally is prescribed the most in the 1st line. From this research and from literature [3], it turns out that treatment with MTX is effective in most cases. This statement does not apply for the systemic subtype of JIA, since they are treated with a biological DMARD in the 1st line [1]. In Figure 3, canakinumab is in the 1st line treatment circle, which is unexpected, because of the high costs for canakinumab. Treatment with canakinumab for systemic JIA patients is more likely when other biological DMARDs are not sufficient. An explanation for the fact that canakinumab is in the 1st line treatment circle, is that these patients were taking part in a study into canakinumab. Canakinumab is in most of the cases prescribed within a study context.

Within the database, 20 different (combinations of) pharmacological treatment options were used as 1st line treatment, as compared with 35 (combinations of) pharmacological treatment in the 2nd line. On average, patients receive 2.3 lines of treatment during an average follow-up period of 4.4 years. The high number of treatment options available, combined with the multiple lines of treatment patients receive emphasizes the complexity in the drug treatment of a JIA patient.

Medication costs

From Table 3 it can be concluded that the average costs per patient per year are by far the highest for the systemic subtype, since biological DMARDs are used in the 1st line for this subtype of JIA [1]. The IQR 25% is €0 for most subtypes. This can be explained by the fact that there are patients who did not receive any drug treatment. A possible explanation for this could be that the drugs are prescribed before or after the analysis period or that the patient was in remission during the analysis period.

Figure 4 shows the proportion of the average annual medication costs per patient attributable to biological DMARDs versus all other medication (i.e. non-biological DMARDs, steroids, depots and the medication from the four categories of medication from the pharmacy registry), per JIA subtype. From Figure 4, it can be concluded that for most subtypes of JIA, the costs for the biological DMARDs are much higher than the costs for all other medication.
For JIA uveitis, the costs for all other medication are higher than the costs for biological DMARDs. These high costs are explained by the fact that patients with uveitis (without joint inflammation) commonly do not use biological DMARDs, but do use eye drops frequently.

Table 4 shows that biological DMARDs are the most expensive group of medication in almost all subtypes of JIA. The biological DMARDs are a relative new group of medication in the treatment of JIA patients. These high costs are partly explained by the patent on these new drugs. Another explanation for the high costs can be the relative small target group for these drugs [9]. Steroids are widely applicable for multiple diseases, the biological DMARDs are often only suitable for treating JIA. Furthermore, the production of biological DMARDs is complex and this together with the small target group could also explain the high costs for biological DMARDs. Patents on biological DMARDs

are going to expire and also biosimilars are introduced. These developments can cause changes in the prices for biological DMARDs in the future.

The average amount of days used per year for non-biological DMARDs and biological DMARDs is approximately the same (81 vs 85 respectively), but the costs per year are much higher for biological DMARDs (€2,500) compared to non-biological DMARDs (€100). This comparison demonstrates that biological DMARDs are much more expensive than non-biological DMARDs. As stated before, the patent on biological DMARDs or the small target group for which they are applicable can be possible explanations for the high price for biological DMARDs.
From Figure 5 it can be concluded that subcutaneous MTX is used for fewer days per year than MTX orally (approximately 100 and 130 respectively), but the total costs per patient per year for subcutaneous MTX are higher than for MTX orally (approximately €50 and €10 respectively), which can be seen in Figure 6, owing to the lower unit costs of MTX orally. Therefore, most patients receive MTX orally as 1st line treatment instead of MTX sc. A switch to subcutaneous MTX can be necessary, when the side effects of MTX orally lead to discomfort for the patient or when MTX orally is not sufficient to reach the desired effect.
An explanation for the higher costs for subcutaneous MTX compared to MTX orally cannot be retrieved from the used dataset. Possible explanations could be the different mode of administration or more expensive ingredients in subcutaneous MTX compared to MTX orally.

In Table 5, it can be seen that canakinumab is by far the most expensive biological DMARD when looking at the average costs per patient per year. In Table 5, also the average total costs per patient, average length of follow-up in years and the total costs per year are displayed.
To calculate the average costs per patient per year, first the costs per year for each individual patient were determined. The costs per year were calculated by dividing the total costs by the follow-up period in years for that patient. The numbers in Table 5 are only the averages. This explains the fact that dividing the average total costs per patient by the average length of follow-up in years does not give the average costs per patient per year.
The total costs per year for all patients together are displayed to determine the overall most expensive drug for the hospital. These total costs are determined by first calculating the total costs for each individual patient and summing all these values. Multiplying the number of patients with the average total costs per patient per year does therefore not give the correct value for the total costs per year for all patients together. From Table 5, it can be concluded that the largest part of the expenditure is spent on adalimumab. This can be explained by the high number of patients who receive treatment with adalimumab.

Strengths and limitations of the study
A strong point of this study is that the costs per patient per year are calculated over a follow up period of multiple years. In these years, there were also periods in which there was no treatment. No treatment means that the patient was in remission. This combination of episodes with and without treatment gives a realistic representation of the costs for a JIA patient.

Another strength of this study is that all subtypes of JIA and all biological DMARDs are compared. In other studies about medication use of JIA patients, often one subtype of JIA or one biological DMARD is considered, which complicates cost comparisons across subgroups. Furthermore, the used database is recent, from 1 April 2011 till 9 April 2019. This gives a realistic representation of the costs for drug treatment of JIA patients. However, some treatment strategies from some years ago, such as stem cell transplantations, can already be outdated nowadays.

A limitation of this study is that for the biological and non-biological DMARDs and steroids no prescribed doses are known. To calculate the total costs, the average of all costs which can be found for all possible doses is used. However, this average is based on information about doses from the

printout of the pharmacy, so the average is quite reliable. The data from the pharmacy is not used to calculate the costs for biological and non-biological DMARDs and steroids, because the start and stop dates are not that reliable compared to the file with only the biological and non-biological DMARDs and the steroids. Also not all prescribed biological and non-biological DMARDs and steroids were included in the pharmacy registry. This is the reason why it was not possible to combine the DMARD and pharmacy registry to calculate the costs for the biological and non-biological DMARDs and steroids.

Another limitation is that for many prescriptions the start and stop dates were unknown. These start and stop dates were filled in manually and are set on the first day of the month or even on the first day of the year. This could have led to an overestimation of the total costs. However, this method is only applied for the relatively low-cost medication, not for biological and non-biological DMARDs and steroids. The start and stop dates which were missing for biological and non-biological DMARDs and steroids were looked up in the patient files and therefore these dates were correct and there is no overestimation of the costs.

Comparison to other studies

Three studies are found in which costs per patient per year for certain biological DMARDs are reported. These costs can be compared to the costs mentioned in Table 5. The studies of Shepherd et al. from 2016 [10] and Prince et al. from 2011 [11], mention the costs for etanercept. Shepherd et al. mentions costs of €10,478.00 per patient per year and Prince et al. mentions costs between €10,448.90 and €10,508.50. The current study found costs of €3,513 per patient per year for etanercept.

The research from Ungar et al. from 2011 [12] mentions the costs per patient per year for abatacept iv, infliximab, etanercept and adalimumab. These costs are €14,733.00, €17,259.00, €18,966.00 and €18,654.00 respectively. In this research, costs of respectively €1,090, €858, €3,513 and €6,491 per patient per year were found.

The costs per patient per year for these biological DMARDs mentioned in this research are all lower than the costs mentioned in the articles.

An explanation for these differences could be that the three studies give the costs for a fulltime year of treatment without periods of no treatment. Patients were only included during periods of active disease. The current study used real patient data from the Wilhelmina Children's Hospital and with this data, the average costs per patient per year were calculated. In this data, there were also periods with no treatment, for example when a patient is in remission. This explains the lower costs in this research compared to the studies of Shepherd et al., Prince et al. and Ungar et al.

The research of Kuhlmann et al. from 2016 [13] reports the average costs per JIA patient per year for all prescribed medication together. These costs vary between €6,227.00 and €15,522.00.

The research of Angelis et al. from 2016 [14] also reports the average costs per JIA patient per year for all medication together. The mentioned costs are €6,667.00.

Average costs of €3,169 per patient per year over all subtypes of JIA were found in this research. This is again much lower compared to the costs mentioned in the studies of Kuhlman et al. and Angelis et al. In these two studies, the costs are again for a fulltime year of treatment, with no episodes of remission. This explains the lower costs mentioned in this research.

Implications for practice

In the past years, the patent for certain biological DMARDs, like adalimumab, has expired. This causes a decrease in the price for these drugs. Also biosimilars, drugs with the same effect as biological DMARDs, but which are cheaper, can decrease the costs for drug treatment of JIA patients. Since this research is about treatment for children, the impact of these price changes on medication prescription patterns is expected to be limited. When a certain treatment for a child is effective, it is not likely that a paediatric rheumatologist will change this treatment. However, for new JIA patients,

these changes can have an effect. Paediatric rheumatologists can for example start with a biosimilar instead of a biological DMARD for a newly diagnoses systemic JIA patient.
Results showed that MTX treatment for patients with polyarticular JIA RF negative is not as effective compared to other subtypes of JIA. This could implicate that for this subtype of JIA a switch to biological DMARDs should be made in an early stage of the treatment.

Recommendations for further research
In this research the costs per subtype of JIA and per biological DMARD are determined. For further research it would be useful to look at possible recommendations regarding which drug should be prescribed to which (group of) patients. These recommendations could be formulated by comparing subgroups in which a certain drug is effective with subgroups in which the same drug is not effective. Subgroups can be based on age, gender, JIA subtype or on certain biomarkers. With these recommendations, the amount of necessary switches in prescribed drug(s) can be reduced and this leads to a decrease in the costs and to less discomfort for the patient.

Furthermore, it would be useful to look at effects of treatment. In this research, only the costs are considered, but the effects are also important. When the effects are good, the wellbeing of the child is increased. When these desired effects imply high costs, is the treatment then justified on macro-economic scale? And when is the limit reached? Incremental cost-effectiveness ratios (ICERs) for certain biological DMARDs (i.e. adalimumab, etanercept and tocilizumab) versus MTX were calculated. These ICERs were £38,127, £32,526 and £38,656 (approximately €42,500, €36,000 and €43,000 respectively) per quality-adjusted life year (QALY) [15]. In the Netherlands, a maximum ICER threshold of €80,000 per QALY is used for diseases that cause a very high proportional loss of remaining health. For less severe diseases, the ICER threshold is €20,000 per QALY [16]. The question is therefore in which category JIA can be classified, severe or less severe diseases. When that question is answered, the ICER threshold can be determined and whether or not the biological DMARDs are cost-effective compared to MTX.

Conclusion

Drug treatment for JIA patients is complex and it is hard to determine the best treatment to achieve control of the disease. On average, patients receive 2.3 lines of treatment during their follow-up.
As expected, drug treatment for JIA patients is by far the most expensive for patients with systemic JIA. This is explained by the fact that patients with systemic JIA receive biological DMARDs as 1st line treatment, in contrast to patients with other JIA subtypes who (in general) start with a non-biological DMARD.
Within the non-biological DMARDs, MTX is the drug which is used most frequently. Oral MTX is much cheaper compared to subcutaneous MTX.
Treatment with MTX is often not successful in patients with RF negative polyarticular JIA.
The probability of successful 1st line treatment is 46.7% and of successful 1st line MTX treatment 65.1% (for nine subtypes of JIA, systemic JIA excluded). Systemic JIA patients are treated with biological DMARDs in the 1st line. Biological DMARDs are the most expensive subgroup of medication in this research. From the biological DMARDs, canakinumab has the highest average costs per patient per year. Adalimumab has the highest total costs per year for all patients together.
For the future it would be useful to formulate recommendations and to look at the effects of treatment.

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Appendix

Appendix A – method to answer the two question for the sequence of medication use for DMARDs and steroids

1. **Are there any patient characteristics which may explain an increased probability of successful 1st line MTX treatment?**
   In the sequence of medication use for DMARDs and steroids, only the patients who received biological and/or non-biological DMARDs and/or steroids are used, because all other patients did not receive any DMARDs. Additional columns were created in Excel to display with "YES" or "NO" if MTX was used in the 1st line treatment, if MTX was used in the 2nd line treatment and whether or not there was a switch from MTX in the 1st line to something else than MTX in the 2nd line treatment. Treatment with MTX can be both orally or subcutaneously (sc). The patients with "YES" in the column for switch from MTX in the 1st line to something else than MTX in the 2nd line were the patients which are being used to answer this question. A switch from MTX orally to MTX sc or vice versa was not considered as a switch.
   Patient characteristics were added to the Excel file. For each characteristic, the mean value and standard deviation were determined and for each subtype based on diagnosis, BMI category and region, the percentages were determined.
   Two subgroups were created in R studio version 3.5.1 (2018-07-02) [8]: a subgroup with only patients who received MTX in the 1st line treatment and a subgroup with patients who received MTX in the 1st line treatment and another drug in the 2nd treatment. For these subgroups again the mean values and percentages for the characteristics were determined and the percentages for each subtype based on diagnosis.
2. **What is the probability of successful 1st line treatment for all JIA patients? And for only systemic JIA patients? And for the other nine subtypes of JIA together?**
   - **What is the probability of successful 1st line treatment with MTX for all subtypes, except systemic JIA, together?**

Successful 1st line treatment means that there is no switch in prescribed drug(s) after the 1st prescribed drug(s). Successful 1st line MTX treatment means that the patient received MTX after diagnosis and there is no switch in prescribed drug(s) after that.

Appendix B – method to correct the start and stop date for the drugs in the pharmacy registry

When subtracting the start date from the end date, the total amount of days that a certain drug was used was calculated. In some cases, there was a negative amount of days. The assumption was made that in those cases the start and end date were turned around. So by taking the absolute value of the end date minus start date, this problem was solved.

Another problem was that some drugs were prescribed for over 30,000 days (82 years). This was obviously a mistake. In most of these cases, the end date was set at 01-01-2099. The assumption was made that this means that the drug was still being used by the patient. For these lines, the end date was set at the day the database was provided, at 09-04-2019. For some other lines, the start date was set at 01-01-2099. In those cases, the start and end date were switched around. For those lines, the end date was set 09-04-2019 and the start date was set at the date which was set as end date.

Another problem was that for some lines, the start and end date was set at 01-01-2099. It was impossible to find out what the correct start and end dates were for these lines. Therefore, it was assumed that these drugs were taken for only one day, like it was in the database, and therefore the start and end date were set at 09-04-2019.

The only remaining problem was that in some lines the end date was not filled in. The assumption was made that this means that the patient was still using this drug. Therefore, the end date was set at 09-04-2019 in those cases.

Appendix C – method to calculate the costs per day for certain categories of drugs

1. Capsules: the costs displayed in the Dutch Pharmacotherapeutic Compass [6] were already the average costs per day based on the average dose for children.
2. Nose/eye drops: the average amount of drops per day was determined from the database. The volume of one flask is known and with the assumption that one drop is 0.05ml, the total amount of days that one flask can be used was calculated. By dividing the costs for one flask by the total amount of days that one flask can be used, the costs per day can be calculated.
3. Concentrations for injections/oral intake: the average amount in milligram that a patient needs to inject each day was determined from the database. The concentration of the prescribed medication was known in milligram/millilitres. With these two numbers, the required volume in millilitres was calculated. It was also known which volume the flask contains and therefore the total amount of days that one flask can be used was calculated. With this amount of days, the costs per day were calculated.
4. Salves: for the salves it was hard to determine how long one package can be used, because it was not stated how many salve is used on one day. Therefore, the assumption was made that one package can be used for fourteen days. The costs were divided by fourteen to calculate the costs per day.

Appendix D – list of DMARD and steroid medication and the subgroup it belongs to and a sunburst chart for these subgroups

Table 6: List of DMARD and steroid medication and the subgroup they belong to

DMARD	Subgroup
Abatacept iv	Biological DMARD
Abatacept sc	Biological DMARD
Adalimumab	Biological DMARD
Anakinra	Biological DMARD
Canakinumab	Biological DMARD

Etanercept	Biological DMARD
Golimumab	Biological DMARD
Infliximab	Biological DMARD
Sarilumab	Biological DMARD
Tocilizumab sc	Biological DMARD
Tocilizumab iv	Biological DMARD
Ustekinumab	Biological DMARD
Azathioprine	Non-biological DMARD
Ciclosporine	Non-biological DMARD
Hydroxychloroquine	Non-biological DMARD
Leflunomide	Non-biological DMARD
Methotrexate orally	Non-biological DMARD
Methotrexate sc	Non-biological DMARD
Mycophenolate mofetil	Non-biological DMARD
Sirolimus	Non-biological DMARD
Sulfasalazine	Non-biological DMARD
Tofacitinib	Non-biological DMARD
Depomedrol im	Steroid
Dexamethason orally	Steroid
Hydrocortison	Steroid
Methylprednisolone iv	Steroid
Prednisolone	Steroid
Prednisolone orally <7.5 mg	Steroid
Prednisolone orally >30 mg	Steroid
Prednisolone orally 7.5 - 30 mg	Steroid

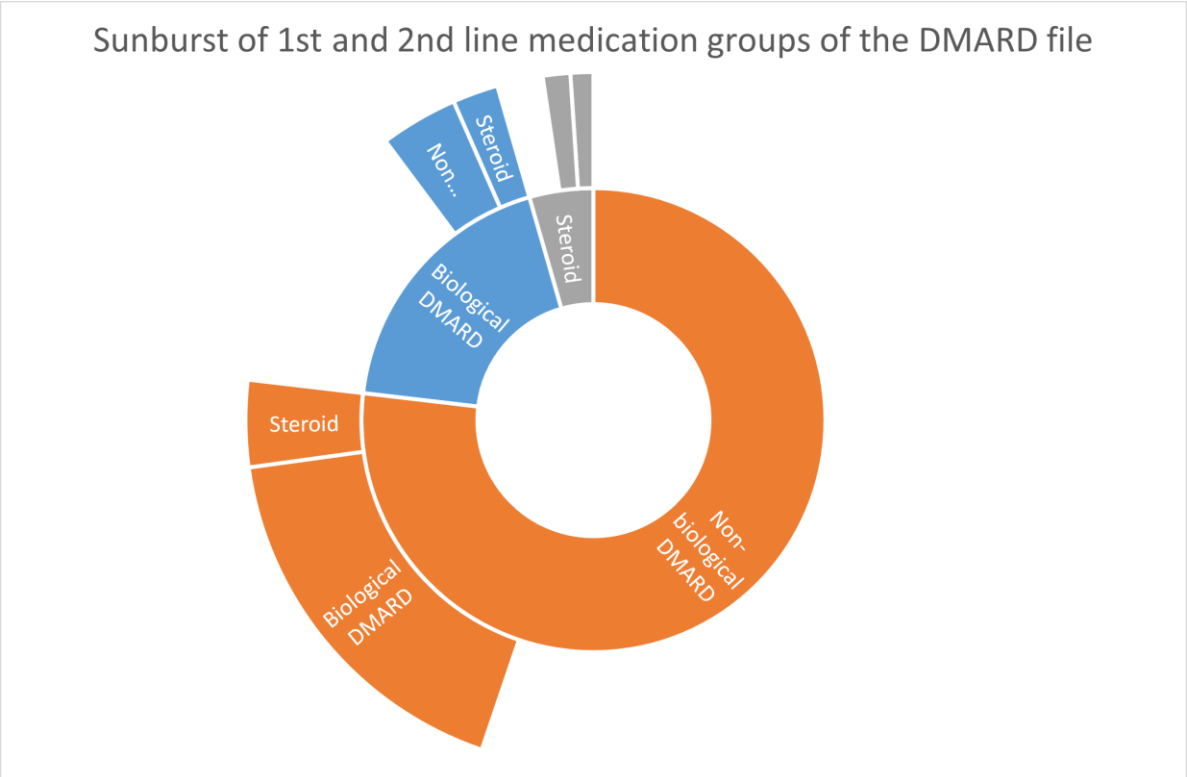

Figure 7: Sunburst chart of the 1st and 2nd line treatment with the three medication groups of the DMARD file

Appendix E – visualization of Table 4

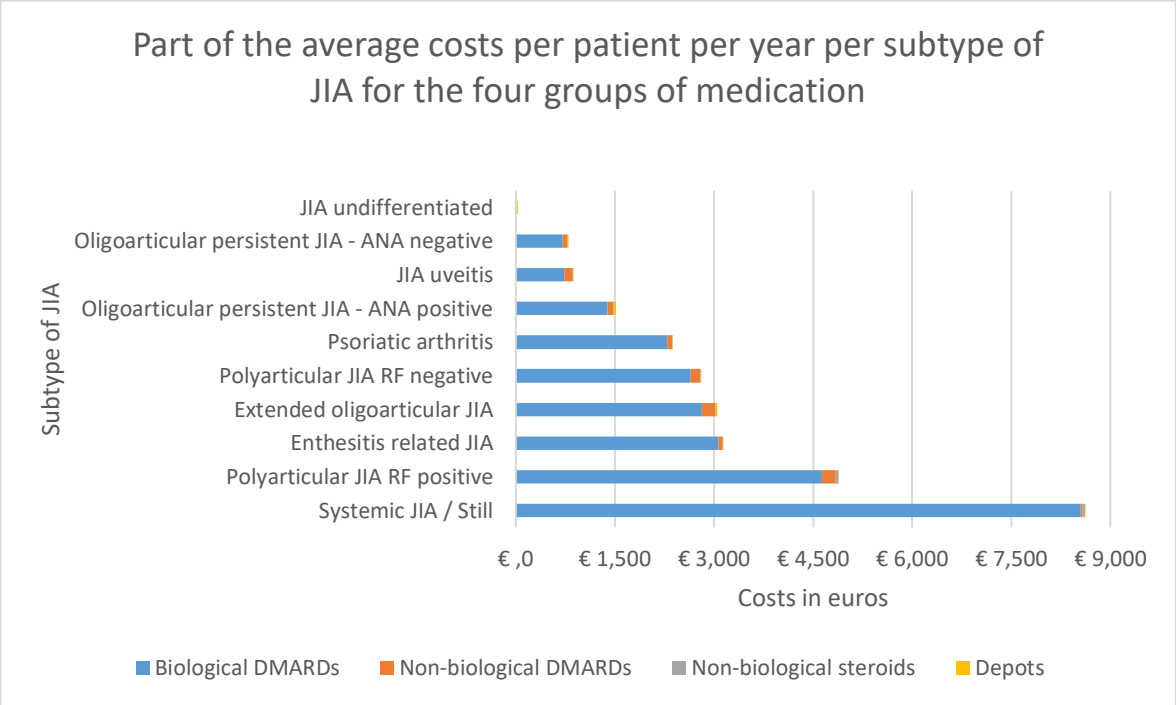

Figure 8: Part of the average costs per patient per year per subtype of JIA for biological and non-biological DMARDs, steroids and depots.