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PAPER

Quantifying the cost impact of withdrawing biologic TNF-α DMARDs in children with juvenile idiopathic arthritis

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Abstract

Background: The cost impact of withdrawing biologic DMARDs (bDMARDs) in JIA patients in clinically inactive disease is currently unknown. The aim of this study is to quantify the difference in costs from a societal perspective of hospital-associated resource (including medication use) between the period before starting TNF-α bDMARDs withdrawal and the two years after starting TNF-α bDMARDs withdrawal (abrupt discontinuation vs. taper) in JIA patients <18 years old, after they achieved clinically inactive disease on TNF-α bDMARDs.
Methods: This study is a retrospective analysis of prospective data from electronic medical records of JIA patients treated in the Wilhelmina Children's Hospital (Utrecht, the Netherlands), aged <18 years between 8 April 2011 and 8 April 2022, and treated with TNF-α bDMARDs, which were abruptly discontinued or tapered during this period. The hospital-associated resource (including medication use) from a societal perspective were extracted during 1) the period of clinically inactive disease (i.e. pre-withdrawal) and compared to the costs within 2a) the first after starting TNF-α bDMARDs withdrawal (i.e. first year post-withdrawal) and 2b) the second year after starting withdrawal (i.e. second year post-withdrawal). All costs were documented as mean annual costs for the following categories: total, medication, rheumatology visits and telephone consultations, radiology investigations, laboratory testing, hospitalisations, and procedures under anaesthesia. The paired t-test was used to evaluate the significance of the difference in costs between the 1) pre-withdrawal period and 2a) first year post-withdrawal and 2b) second year post-withdrawal. Moreover, a subgroup analysis was conducted to evaluate the annual cost differences between patients who abruptly discontinued TNF-α bDMARDs and patient who tapered TNF-α bDMARDs, using the Mann-Whitney U test. In addition, two deterministic sensitivity analyses were performed to test the robustness of the results, and the analysis is conducted from a hospital perspective, in which societal costs were excluded. All tariffs were obtained from the Dutch Costing Manual, Dutch Healthcare Authority and National Health Care Institute.
Results: 56 patients with JIA were included of whom 26 abruptly discontinued and 30 tapered TNF-α bDMARDs. The mean annual total costs per patient are €9,856 in the pre-withdrawal period (mean follow-up of 428 days) and decrease significantly to €5,305 (-46.2%, $p<0.05$) in the first year post-withdrawal period and significantly to €7,153 (-27.4%, $p<0.05$) in the second year post-withdrawal. 7.3%, 15.3% and 9.6% of these annual costs can be attributed to societal costs in the pre-withdrawal period, first year post-withdrawal and second year post-withdrawal, respectively. The medication accounts for the majority of the total costs, namely 82.1%, 63.2% and 76.9% for the pre-withdrawal period, first year post-withdrawal period and second year post-withdrawal period, respectively. When distinguishing between withdrawal strategies, mean annual costs per patient within the first year post-withdrawal reduce by 57.6% and 36.2% compared to the pre-withdrawal period, for the abrupt discontinuation and taper group, respectively. In the second year post-withdrawal, the mean annual costs reduce by 30.2% and 24.8% compared to the pre-withdrawal period for the abrupt discontinuation and taper group, respectively. However, the abrupt discontinuation group and taper group do not significantly differ in cost differences between the 1) pre-withdrawal period and 2a) first year post-withdrawal and 2b) second year post-withdrawal.
Conclusions: Withdrawing TNF-α bDMARDs is cost-saving compared to the period before starting TNF-α bDMARD withdrawal in JIA patients <18 years old, after they reached clinically inactive disease on TNF-α bDMARDs. Greater cost reductions are found between the pre-withdrawal period and first year post-withdrawal than between the pre-withdrawal period and second year post-withdrawal, especially for the patients who abruptly discontinued TNF-α bDMARD use. The two withdrawal strategies (i.e. abrupt discontinuation vs. taper) do not differ significantly in achieved cost reductions.

Key words: JIA; withdrawal of TNF-α bDMARD; cost impact; treatment; clinically inactive disease; abrupt discontinuation vs. taper; children

Key Points

- The mean annual JIA-related costs are €9,856 per patient and reduce significantly to €5,305 and €7,153 within the first year post-withdrawal and second year post-withdrawal, respectively, of TNF-α bDMARDs, corresponding to a reduction of 46.2% and 27.4% compared to the period before starting TNF-α bDMARD withdrawal.
- The majority of the costs are attributable to medication, namely 82.1%, 63.2% and 76.9% for the pre-withdrawal period, the first year post-withdrawal and the second year post-withdrawal, respectively.
- The greatest costs reductions are found within the first year after starting TNF-α bDMARD withdrawal, especially for the patients who abruptly discontinued TNF-α bDMARDs, resulting in a mean annual cost reduction of 57.6% within the first year after starting TNF-α bDMARD withdrawal compared to the period before starting withdrawal.
- The withdrawal strategies (abrupt discontinuation vs. taper) do not differ significantly in cost differences between the period before starting TNF-α bDMARD withdrawal and after starting TNF-α withdrawal.

Background

Juvenile idiopathic arthritis (JIA) is a blanket term for all arthritic diseases lasting a minimum of six weeks with an unknown aetiology, diagnosed in childhood [1]. JIA is the most common chronic inflammatory disease in children. In the Netherlands, 2,000-3,000 children are diagnosed with JIA, which equates to a prevalence of 0.8-1.0 per 1,000 children [2]. JIA includes several subtypes with different clinical manifestations, including symptoms such as joint swelling, joint stiffness, joint pain, fatigue, fever and uveitis [2, 3]. In the long-term, JIA can result in growth abnormalities and mental disabilities, such as stress, depression, and anxiety, which in turn result in lower educational levels and a decreased quality of life [4, 5, 6, 7]. In addition, the burden and impact on caregivers and family are substantial, negatively affecting their quality of life, productivity and social well-being [8, 9].

Adequate treatment of JIA is needed to reduce the patient's symptoms, restore their physical and psychological functioning, and thereby prevent or limit long-term joint damage and disability [10, 11]. The treatment of JIA is often multidisciplinary, including both pharmacological therapy, physical therapy, occupational therapy, and psychosocial support [12]. Commonly used medicines in pharmacological therapy are non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). Pharmacological therapy of JIA treatment accounts for approximately 50% of the total treatment costs [13]. This ratio, as well as the number of treatment options, have significantly increased with the development of a new class of drugs two decades ago: biological disease-modifying anti-rheumatic drugs (bDMARDs). The most commonly used bDMARDs are TNF-α bDMARDs, specifically the TNF agents adalimumab and etanercept [14]. bDMARDs are highly effective in reducing symptoms and significantly improve long-term outcomes [2, 15]. However, bDMARDs are costly compared to the other pharmacological therapies in JIA, attributing to 91.8% of the total costs of pharmacological therapy in JIA [16]. In addition, JIA patients often consider the administration of bDMARDs (subcutaneously or intravenously) as invasive and experience potential side effects of DMARD use, such as nausea, headache, and being more prone to infections.

Due to the high cost of bDMARDs, the burden of bDMARD injections on patients, and potential side effects, withdrawing bDMARDs is often attempted after the JIA has been clinically inactive for a period of time [17]. Two withdrawal strategies can be distinguished: 1) abrupt discontinuation of bDMARDs and 2) tapering bDMARDs, which in this paper encompasses: i) gradually increasing the time interval between two administrations, and ii) gradually decreasing the dose that is administered [18]. However, in about two-third of the patients, withdrawal of bDMARDs causes the disease to flare up within one year, leading to additional strain on the patient and possible joint damage [19, 20, 21]. Flares also cause extra hospital-associated resource use and accompanying costs, attributable to extra rheumatology visits, hospitalisations, and they may require restarting, intensifying or changing medication. As a consequence, it is currently unknown what the cost impact of withdrawing bDMARDs is in JIA patients after they reached clinically inactive disease. Moreover, there is a lack of knowledge about the effect of the withdrawal strategy (i.e. abrupt discontinuation vs. taper) on costs and effectiveness.

The aim of this study is to quantify the difference in costs of JIA-related care in the period before withdrawing TNF-α bDMARDs and within two years after starting TNF-α bDMARD withdrawal, in JIA patients <18 years old, after they reached clinically inactive disease on TNF-α bDMARDs. In this study, the post-withdrawal period is split into the first and second year after starting TNF-α bDMARD withdrawal to provide insight in the cost impact of TNF-α bDMARD withdrawal over time. In addition, a subgroup analysis is conducted to compare the cost impact of the two withdrawal strategies, i.e. abrupt discontinuation vs. taper of TNF-α bDMARDs.

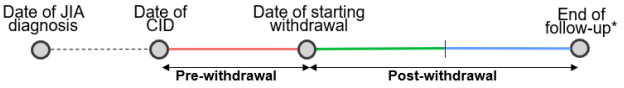

Figure 1. Time path of the follow-up period. The pre-withdrawal period captures the whole period of clinically inactive disease (CID) until the date that withdrawing TNF-α bDMARD is started (red line). The post-withdrawal period starts from the moment TNF-αbDMARD withdrawal is started, lasting up to *) two years, or until the patient turns eighteen, or transitions to another hospital, with a minimum of one year of follow-up. The post-withdrawal period is split into the first year post-withdrawal (green) and the second year post-withdrawal (blue).

Method

In this study, the costs of JIA-related care were determined using a bottom-up patient level costing approach from a societal perspective, incorporating hospital-associated care costs (including medication costs), and societal costs for hospital visits in terms of i) travel costs, ii) costs for labour productivity losses of the caregiver attending the hospital visits and iii) parking costs. The costs

per patient were determined in 1) the period of clinically inactive disease (defined as the "pre-withdrawal" period) and compared to: 2a) the costs within the first year after starting TNF-α bDMARD withdrawal (i.e. "first year post-withdrawal" and 2b) the costs within the second year after starting TNF-α bDMARD withdrawal (i.e. "second year post-withdrawal"), as shown in Figure 1. The pre-withdrawal period started from the date that the paediatric rheumatologist assessed that the JIA was clinically inactive, which means that the patient had: 1) no swollen joints, 2) no joints with both loss of range of motion and joint pain, 3) a score of zero on the physician's global assessment scale. The date of clinically inactive disease was manually extracted from the patients' electronic medical records. The pre-withdrawal period captured the whole period of clinically inactive disease until the start of TNF-α bDMARD withdrawal. In contrast, the post-withdrawal period started from the start of TNF-α bDMARD withdrawal, lasting up to two years, or shorter when the patient turned eighteen or transitioned to another hospital in this period.

Patient inclusion

Patients were included if they were treated for JIA in the Wilhelmina Children's Hospital (Utrecht, the Netherlands), were aged <18 years old between 8 April 2011 and 8 April 2022, and treated with TNF-α bDMARDs, which were abruptly discontinued or tapered during this time period. The starting date of 8 April 2011 was chosen because the data used in the analysis were only available in electronic form after this date. Patients were excluded if: 1) JIA was not the primary reason for TNF-α bDMARD prescription, 2) the patient was diagnosed with systemic JIA (sJIA), 3) the patient had a follow-up of less than one year after starting TNF-α bDMARD withdrawal (e.g. due to turning eighteen or transitioning to another hospital). In addition, patients who had less than six months of follow-up in the second year post-withdrawal (i.e. 1.5 years from starting TNF-α bDMARD withdrawal) were excluded from the second year post-withdrawal analysis but remained included in the pre-withdrawal and first year post-withdrawal.

Resource use

The JIA-related hospital-associated resource and medication use were obtained via a retrospective analysis of prospective data from electronic medical records of JIA patients for each of the three time periods (pre-withdrawal, first year post-withdrawal, second year post-withdrawal). In addition, travel distance and time, hours of labour productivity losses and parking time were determined on a patient level per hospital visit.

Hospital-associated resource and medication use

The hospital-associated resource use was extracted on a patient level from the electronic medical records for the following resource use categories: rheumatology visits, telephone consultations, radiology investigations, laboratory testing, hospitalisations and procedures under anaesthesia. Only JIA-related hospital-associated resource use was included. To illustrate this, only laboratory testing and radiology investigations, which were judged to be JIA-related according to a paediatric rheumatologist were included. Additionally, hospitalisations and procedures under anaesthesia, which were judged to be directly related to JIA care according to a paediatric rheumatologist were included. In case of doubt, a second paediatric rheumatologist was consulted. Furthermore, only hospital visits to the paediatric rheumatology department and telephone consultations with paediatric rheumatologists were included in the analysis.

The medication use was extracted manually from the patients' electronic medical records. For each medicine, the following data were extracted: start date, stop date, dose and administration interval. Medicines included in the analysis were bDMARDs, csDMARDs and corticosteroids (articular injections and oral administration). NSAIDs were excluded from the analysis because these are over-the-counter medications in the Netherlands and therefore their use is not properly recorded. A detailed overview of all inclusion criteria and assumptions made regarding hospital-associated resource use and prices is provided in Appendix A.

Travel, labour productivity losses and parking

The travel use, hours of labour productivity losses and parking time were manually extracted on a patient level from the electronic medical records per hospital visit. First, the travel distance was approximated on a patient level using the four letter digit of the postal codes of the patients' residential address and the Wilhelmina Children's Hospital. Subsequently, the travel time was estimated using Google Maps. Second, the lost labour productivity time for the caregiver was determined by incorporating both travel time and the estimated time spent in the hospital. The time spent in the hospital was assumed to be two hours for rheumatology visits, which may also include radiology investigations or laboratory testing, and was determined on a patient level from the data for hospitalisations and procedures under anaesthesia. For all hospital visits, it was assumed that one caregiver attended the patient during the hospital visits. Third, parking time was equated to the time spent in the hospital. For telephone consultations, lost labour productivity time was assumed to be 20 minutes per telephone consultation. Travel time and parking time were not included for telephone consultations, assuming telephone consultations take place from home.

Resource use costs

The unit costs used in the current study were based on the guidelines of the Dutch Costing Manual [22]. All tariffs were converted to 2022 Euros using Dutch consumer price indices. No discounting has been applied in the cost calculations.

Hospital-associated resource use and medication use

The costs for the rheumatology visits (€112.17) and hospitalisation (€696.32) were based on the tariffs for a paediatric department visit as reported in the Dutch Costing Manual [22]. Telephone consultations were valued as 50% of the costs per paediatric department visit, equalling €56.09 per telephone consultation [22]. Costs for hospitalisations associated with intravenous bDMARD administration were set to €408.33, in line with the Dutch Healthcare Authority [23]. Costs for laboratory testing, radiology investigations, and procedures under anaesthesia were obtained from a previous study by Kip et al. (2021), in which Dutch Healthcare Authority tariffs were used [24]. Medication costs were obtained from the Dutch pharmaceutical list prices as reported by the National Health Care Institute, as shown in Appendix B [25]. Moreover, a dispensing fee (€6) was charged when a patient starts with a medicine and was repeated every 90 days, because this is the maximum time period over which the pharmacy is allowed to dispense medication [22].

Travel, parking and labour productivity losses

The costs per travel kilometer (€0.21) and the costs per hour of lost labour productivity (€38.36) were based on the Dutch Costing Manual [22]. The parking costs were set to €1.80 per hour, as reported by the Wilhelmina Children's Hospital [26].

Analysis

The analysis was performed in R version 1.4.1717, using the packages birk, dplyr, ggplot2, lubridate and plotrix [27, 28, 29, 30, 31]. The total costs per patient were determined by multiplying the unit costs with the patient's JIA-related resource use. The costs were reported as annual costs in euros per patient for each of the three defined time periods: 1) the pre-withdrawal period, 2a) the first year post-withdrawal, and 2b) the second year post-withdrawal. The total annual costs per period were visualised using boxplots. In addition, the annual costs were split into different categories, namely medication, rheumatology visits and telephone consultations, radiology investigations, laboratory testing, hospitalisations and procedures under anaesthesia. The annual costs were reported for the total group (all included patients) and stratified according to the withdrawal strategy used in a subgroup analysis (i.e. abrupt discontinuation vs. tapering).

The paired t-test was used to evaluate the significance of the mean difference in total annual cost, and the Mann-Whitney U test was used to compare the cost differences between the two subgroups (abrupt discontinuation vs. taper) between the 1) pre-withdrawal period and 2a) first year of the post-withdrawal period and 2b) second year of the post-withdrawal period.

The impact of uncertainty in cost inputs on the cost differences between the pre-withdrawal and post-withdrawal periods was assessed by performing two deterministic sensitivity analyses, in which one (set of) cost parameters was varied at the time by $\pm 25\%$, while all other cost inputs were kept constant. In the first one-way sensitivity analysis, all categories of cost input parameters were varied separately. To illustrate this, all costs associated with radiology testing were increased by 25% and subsequently reduced by 25%. For both changes, the impact on the difference in costs between the pre-withdrawal and the post-withdrawal periods was assessed. In the second one-way sensitivity analysis, the costs per DMARD (both bDMARDs and csDMARDs) were varied by $\pm 25\%$ to determine the attribution of each individual DMARD to the cost differences between the periods. The results were visualised in tornado diagrams. In addition, a scenario analysis was performed to evaluate the results of the analysis if a hospital perspective was used instead of a societal perspective. In this scenario, the travel costs, parking costs and labour productivity losses costs were neglected.

Results

Out of the 257 patients who were treated with TNF-α bDMARDs between 8 April 2011 and 8 April 2022 in the Wilhelmina Children's Hospital, 56 patients were included in the analysis. As illustrated in Figure 2, reasons for excluding patients were for example uveitis as the primary reason for TNF-α bDMARD prescription, no attempt to withdraw TNF-α bDMARD between 8 April 2011 and 8 April 2022, or less than one-year follow-up after starting TNF-α bDMARD withdrawal. Of these 56 included patients, 31 (i.e. 55%) are girls. The median age is 7.5 years (IQR: 3.9-11.5), 10.2 years (IQR: 6.5-13.0), and 11.1 years (IQR: 8.6-14.5) at JIA diagnosis, clinically inactive disease, and starting TNF-α bDMARD withdrawal, respectively. All main characteristics of the included patients, grouped into the total, abrupt discontinuation and taper group, can be found in Appendix C, Table 3. For the second year post-withdrawal analysis, 8 patients were excluded because their follow-up was less than 1.5 year after starting TNF-α bDMARD withdrawal. As a consequence, 48 patients were included for the second year post-withdrawal analysis.

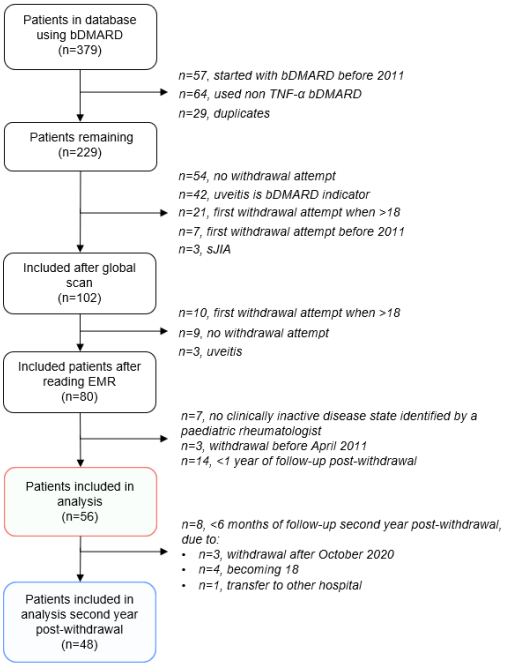

Figure 2. Flowchart patient inclusion. The green box represents the patient who were included in the pre-withdrawal period and first year post-withdrawal. The blue box, represents the patients who were also included in the second year post-withdrawal analysis. sJIA=systemic JIA.

Total group

The mean follow-up in the pre-withdrawal period is 428 days, ranging from 98 to 1913 days. In this period, the mean annual total costs of JIA are €9,856 per patient (n=56). The mean annual total costs reduce significantly to €5,305 in the first year post-withdrawal (n=56, fixed follow-up of 365 days) [$t(55)=7.61$, $p<0.05$]. In the second year post-withdrawal, the mean annual total costs reduce significantly to €7,153 (n=48, mean follow-up of 353 days), [$t(47)=2.96$, $p<0.05$], Table 1. This represents a mean annual reduction of €4,551 (i.e. 46.2%) and €2,703 (i.e. -27.4%) compared to the pre-withdrawal period per patient in the first year post-withdrawal and the second year post-withdrawal, respectively. When looking at the individual patient level, the annual total costs reduce for 95% of the patients (n=53) in the first year post-withdrawal, ranging from cost reductions of €247 to €25,836 per patient. For the three patients whose annual costs increase, the annual cost increment range between €369 to €456. In the second year post-withdrawal, the annual total costs increase for 12 of the 48 patients with respect to the pre-withdrawal period, ranging from €106 to €12,226. In contrast, the cost reductions for the other 36 patients range between €-9 to €-25,414.

For all three periods, the majority of the costs are attributable to medication, namely 82.1%, 63.2% and 76.9% for the pre-withdrawal period, the first year post-withdrawal and the second year post-withdrawal, respectively, Table 1. In the pre-withdrawal period, the remaining 17.9% is attributable to rheumatology visits and telephone consultations (12.3%), hospitalisations (2.3%), laboratory test (2.0%), radiology investigations (1.2%) and procedures under anaesthesia (0.02%). In the first year post-withdrawal, the remaining 36.8% is attributable to rheumatology visits and telephone consultations (25.4%), hospitalisations (5.5%), radiology investigations (3.0%), laboratory testing (2.7%), and procedures under anaesthesia (0.2%). In the second year post-withdrawal, the remaining 23.1% can be attributed to rheumatology visits and telephone consultations (16.4%), radiology investigations (2.6%), labo-

Table 1. Overview of the annual costs (reported as mean (95% confidence intervals)) given per group (total, abrupt discontinuation and taper), period (pre-withdrawal, first year post-withdrawal and second year post-withdrawal) and category (total, medication, rheumatology visits and telephone consultations, radiology investigations, laboratory testing, hospitalisations and procedures under anaesthesia).

Group		Total			Abrupt discontinuation			Taper		
Category \ Period		pre-withdrawal (n=56)	1st post-withdrawal (n=56)	2nd post-withdrawal (n=48)	pre-withdrawal (n=56)	1st post-withdrawal (n=56)	2nd post-withdrawal (n=48)	pre-withdrawal (n=56)	1st post-withdrawal (n=56)	2nd post-withdrawal (n=48)
Total		**€9,856** (€8,887-€10,825)	**€5,305** (€4,451-€6,160)	**€7,153** (€5,871-€8,435)	**€9,843** (€8,117-€11,570)	**€4,172** (€3,081-€5,263)	**€6,866** (€5,094-€8,637)	**€9,867** (€8,850-€10,884)	**€6,287** (€5,111-€7,464)	**€7,417** (€5,542-€9,292)
Medication		€8,090 (€7,215-€8,965)	€3,355 (€2,719-€3,990)	€5,498 (€4,395- €6,600)	€7,929 (€6,263-€9,594)	€2,211 (€1,331-€3,092)	€5,318 (€3,612-€7,024)	€8,230 (€7,468-€8,991)	€4,345 (€3,601-€5,090)	€5,663 (€4,217-€7,108)
Rheumatology visits & TC		€1,217 (€1,088-€1,346)	€1,349 (€1,194-€1,504)	€1,172 (€970-€1,375)	€1,457 (€1,245-€1,668)	€1,489 (€1,235-€1,742)	€1,056 (€882-€1,230)	€1,009 (€897-€1,121)	€1,228 (€1,051-€1,404)	€1,280 (€926-€1,634)
Radiology investigations		€122 (€79-€165)	€159 (€92-€226)	€185 (€125-€245)	€165 (€97-€234)	€196 (€97-€294)	€206 (€111-€301)	€85 (€34-€135)	€127 (€37-€216)	€166 (€91-€241)
Laboratory testing		€195 (€116-€274)	€145 (€104-€187)	€161 (€71-€250)	€236 (€80-€392)	€168 (€90-€246)	€192 (€14-€369)	€159 (€104-€214)	€126 (€90-€161)	€132 (€80-€185)
Hospitalisation		€230 (€0-€627)	€290 (€0-€668)	€132 (€0-€317)	€236 (€80-€392)	€109 (€0-€225)	€84 (€0-€195)	€381 (€0-€1,114)	€447 (€0-€1,141)	€176 (€0-€522)
Procedures under anaesthesia		€2 (€0-€7)	€8 (€0-€19)	€5 (€0-€14)	€0 (€0-€0)	€0 (€0-€0)	€10 (€0-€29)	€4 (€0-€13)	€15 (€0-€36)	€0 (€0-€0)

TC=Telephone Consultation

ratory testing (2.2%), hospitalisation (1.8%) and procedures under anaesthesia (0.1%). The included hospitalisations in the different periods are related to intravenously bDMARD injections and intra-articular injections. In addition, the included procedures under anaesthesia consist exclusively of intra-articular injections under sedation, in all three periods. A more detailed overview of the costs per category for the pre-withdrawal, first year post-withdrawal and second year post-withdrawal is shown in Appendix D, Figure 10.

Figure 3. The annual total costs per period (pre-withdrawal, first year post-withdrawal, and second year post-withdrawal) for the total group, abrupt discontinuation group and taper group. The number in brackets represents the number of patients included in the pre-withdrawal period and first year post-withdrawal. The number in the squared brackets represents the patients included in the second year post-withdrawal.

Subgroup analysis

The counts per appointment type during the follow-up period. Operational contact means that an additional activity took place, for example medication administration during the rheumatology visit. The second aim of this study is to compare the cost differences between the two withdrawal strategies (abrupt discontinuation [n=26] vs. taper [n=30]). During the pre-withdrawal period, the mean annual total costs per patient are €9,843 and €9,867 for the abrupt discontinuation group (mean follow-up of 478 days) and taper group (mean follow-up of 385 days), respectively, Table 1. The mean annual total costs are not significantly different between the abrupt discontinuation group and taper group, as evaluated by using the Mann-Whitney U test [$U(n=26, n=30,)=293.00$, $z=-1.59$, $p=0.11$]. In the first year post-withdrawal, the mean annual total costs reduce significantly to €4,172 (-57.6%) in the abrupt discontinuation group [$t(25)=4.82$, $p<0.05$], and significantly to €6,287 (-36.2%) in the taper group [$t(29)=8.89$, $p<0.05$], Table 1. In the abrupt discontinuation group, the annual total costs range between €0 to €10,126. This variability is mainly attributable to the restart of bDMARDs by 16 of the 26 patients within the first year, who are representing the higher annual costs. In the taper group, the annual total costs range from €1,867 to €19,789, with the lower costs representing patients who tapered TNF-α bDMARD without restarting or re-intensifying bDMARD use within the first year (14 of the 30 patients). On the other hand, the higher costs representing patients who were not able to taper and needed to re-intensify TNF-α bDMARD use (7 of the 30 patients), or patients who restarted bDMARD use after tapering to a complete stop of TNF-α bDMARD use within one year (9 of the 30 patients). However, when comparing the annual total cost differences between pre-withdrawal and the first year post-withdrawal using the Mann-Whitney U test, no significant difference is found between the with-

drawal strategies [U(n=26, n=30,)=323.00, z=-1.10, p=0.27]. In the second year post-withdrawal, the mean annual total costs decrease compared to the pre-withdrawal period for both subgroups, Table 1. In the abrupt discontinuation group, 23 of the 26 patients were included in the second year post-withdrawal, 14 of the 23 patients were using bDMARDs at the beginning of the second year post-withdrawal, and 4 patients restarted bDMARDs during the second year post-withdrawal. For the abrupt discontinuation group, the mean annual total costs reduce by 30.2% to €6,866 compared to the pre-withdrawal period. However, the annual costs in the pre-withdrawal period and the annual costs in the second year post-withdrawal are not significantly different [t(22)=1.79, p=0.09]. In the taper group, 25 of the 30 patients were included in the second year post-withdrawal analysis of who 14 used bDMARD at the beginning of the second year, and 7 patients restarted bDMARD during the second year. For the taper group (n=25), the mean annual total costs decrease significantly by 24.8% to €7,417 in the second year post-withdrawal compared to the pre-withdrawal period [t(24)=2.72, p<0.05]. Similarly as in the first year, the abrupt discontinuation and taper group do not differ significantly in annual cost difference between the pre-withdrawal period and the second year post-withdrawal [U(n=23, n=25,)=254.00, z=-0.69, p=0.27]. The annual total costs per subgroup and per period are visualised in Figure 3.

Sensitivity analysis

The impact of varying cost inputs on the cost differences between the 1) pre-withdrawal period and 2a) first year post-withdrawal and 2b) second year post-withdrawal are presented in Figure 5. As the tornado diagrams illustrate, varying the medication costs by ±25% resulted in maximum changes in cost differences of 26.0% (i.e. ±€1,184) and 24.0% (i.e. ±€648) with respect to the base case cost differences (i.e. €4,551 and €2,703), between the pre-withdrawal period and first year post-withdrawal and the pre-withdrawal period and the second year post-withdrawal, respectively. For the cost difference between the pre-withdrawal period and the first year post-withdrawal, varying the hourly labour productivity costs and the hospitalisation costs resulted in the second (0.4%) and third greatest change (0.3%) with respect to the base case cost difference. For the cost difference between the pre-withdrawal period and the second year post-withdrawal, the variation of the cost inputs for the hospitalisation and radiology resulted in respectively the second greatest change (0.9%) and third greatest change (0.6%) with respect to the base case cost difference. However, in all sensitivity analyses, total costs are lower in both withdrawal periods compared to the pre-withdrawal period. To test the robustness of this result, it was determined what reduction in medication costs would be required to make the withdrawal of medication no longer cost-saving. It was found that the total medication costs should reduce by 94% (i.e. from €8,090 to €315 within the pre-withdrawal period, and from €3,355 to €131 within the first year post-withdrawal) to make withdrawal of medication no longer cost-saving. In the second year post-withdrawal, total costs were found to be lower compared to the pre-withdrawal period regardless of the reduction in medication costs.

The impact of varying the costs of individual DMARDs on the cost differences between the 1) pre-withdrawal period and 2a) first year post-withdrawal and 2b) second year post-withdrawal are presented in Figure 5. As shown in the tornado diagrams, adalimumab is the DMARD with the highest impact on the total cost differences between the pre-withdrawal and both post-withdrawal periods. For the cost difference between the 1) pre-withdrawal period and 2a) first year post-withdrawal, varying the costs by ±25% per DMARD simultaneously results in a change of 17.4%, 7.2% and 1.2% with respect to the cost difference in the base case (i.e. €4,551) for adalimumab, etanercept and golimumab, respectively. For the cost difference between the 1) pre-withdrawal period and 2b) second year post-withdrawal, varying the costs by ±25% per DMARD simultaneously results in a change of 21.0%, 6.3% and 2.2% with respect to the cost difference in the base case (i.e. €2,703) for adalimumab, etanercept, and tocilizumab, respectively. However, by evaluating the ±25% cost inputs for the different DMARD types none of these inputs will result in an increase in costs between the pre-withdrawal period and the post-withdrawal periods.

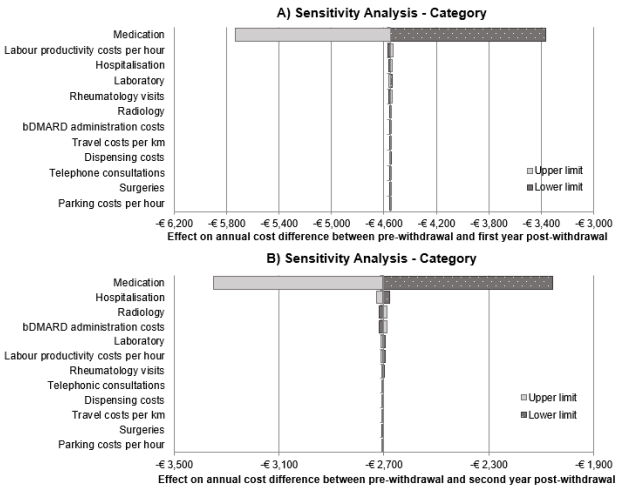

Figure 4. The results of the sensitivity analysis of the different categories of cost inputs. A) the effect of varying the cost inputs per category by [-25% (dark grey dotted), +25% (light grey)] on the mean annual total cost difference between the pre-withdrawal period and the first year post-withdrawal. B) the effect of varying the cost inputs per category by [-25% (dark grey dotted), +25% (light grey)] on the mean annual total cost difference between the pre-withdrawal period and the second year post-withdrawal.

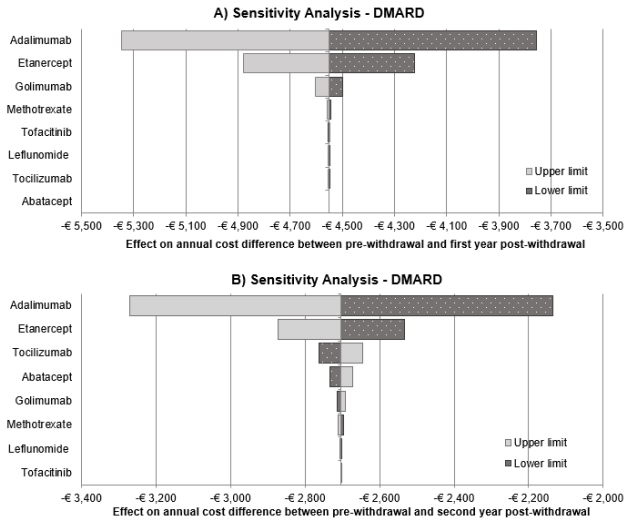

Figure 5. The results of the sensitivity analysis of the DMARD types. A) the effect of varying the cost inputs per DMARD by [-25% (dark grey dotted), +25% (light grey)] on the mean annual total cost difference between the period before starting withdrawal and the first year post-withdrawal. B) the effect of varying the cost inputs per DMARD by [-25% (dark grey dotted), +25% (light grey)] on the mean annual total cost difference between the pre-withdrawal period and the second year post-withdrawal.

Hospital perspective analysis

The mean annual total costs consist of 7.3%, 15.3% and 9.6% of societal costs in the pre-withdrawal period, first year post-withdrawal and second year post-withdrawal, respectively. Therefore, when using a hospital perspective instead of a societal perspective, the mean annual total costs are €9,138, €4,492 and €6,467 for the pre-withdrawal period, first year post-withdrawal and second year post-withdrawal, respectively, as shown in Appendix E, Figure 11 and Table 4. The mean annual costs reduce by 50.8% in the first year post-withdrawal and by 29.2% in the second year post-withdrawal compared to the pre-withdrawal period. Similarly as when using a societal perspective, the cost differences between the 1) pre-withdrawal period and 2a) first year post-withdrawal and 2b) second year post-withdrawal are significant. The medication category attributes to 88.5%, 74.7% and 85.0% to the total costs for the pre-withdrawal period, first year post-withdrawal and second year post-withdrawal, respectively. In the pre-withdrawal period, the remaining 11.5% is attributable to rheumatology visits and telephone consultations (6.1%), laboratory testing (2.1%), hospitalisations (1.9%), radiology investigations (1.3%), and procedures under anaesthesia (0.0%), as shown in Appendix E, Figures 11 and 12 and Table 4. In the first year post-withdrawal, the remaining 25.3% is attributable to rheumatology visits and telephone consultations (14.6%), hospitalisations (4.8%), radiology investigations (3.5%), laboratory testing (3.2%) and procedures under anaesthesia (0.2%). In the second year post-withdrawal, the remaining 15.0% is attributable to rheumatology visits and telephone consultations (8.2%), radiology investigations (2.9%), laboratory testing (2.5%), hospitalisations (1.4%) and procedures under anaesthesia (0.1%). In addition, no significant cost differences between the withdrawal strategies are found between the pre-withdrawal period and first year post-withdrawal [U(n=25, n=30)=315.00, z=-1.23, p=0.22], and the pre-withdrawal period and second year post-withdrawal [U(n=23, n=25,)=247.00, z=-0.84, p=0.40].

Discussion

The present study was performed to determine the effect of TNF-α bDMARDs withdrawal on costs from a societal perspective of JIA care within the first and second year after starting TNF-α bDMARDs withdrawal compared to the period before starting TNF-α bDMARDs withdrawal. The study findings indicate that TNF-α bDMARDs withdrawal significantly reduces the mean annual costs by 46.2% [t(55) = 7.61, p<0.05] and 27.4% [t(47)=2.96, p<0.05] compared to the pre-withdrawal period for the first year post-withdrawal and second year post-withdrawal, respectively. 81.2%, 63.2% and 76.9% of the mean annual costs can be attributed to the medication costs for the pre-withdrawal period, first year post-withdrawal and second year post-withdrawal, respectively. When using a hospital perspective, the cost reduction is also significant both in the first year post-withdrawal (50.8%) [t(55) = 8.20, p<0.05] and in the second year post-withdrawal (29.2%) [t(47) = 3.05, p<0.05] compared to the pre-withdrawal period. In addition, the current study does provide unique insights into the cost reductions of abruptly discontinuing and tapering TNF-α bDMARDs within the first and second year after starting TNF-α bDMARD withdrawal. In the abrupt discontinuation group, the annual costs reduce by 57.6% and 32.0% compared to the pre-withdrawal period in the first year post-withdrawal and second year post-withdrawal, respectively. In the taper group, the annual costs reduce by 36.2% and 24.8% compared to the pre-withdrawal period in the first year post-withdrawal and second year post-withdrawal, respectively. When comparing the two withdrawal strategies (abrupt discontinuation vs. taper), no significant cost differences between the two groups are found between the 1) pre-withdrawal period and 2a) first year post-withdrawal [U(n=26, n=30,)=293.00, z=-1.59, p=0.11], and 2b) second year post-withdrawal [U(n=23, n=25,)=254.00, z=-0.69, p=0.27].

Literature

In accordance with the present results, previous studies have demonstrated that pharmacological treatment, especially bDMARD treatment, is the largest contributor to total costs [13, 32, 33, 34, 35]. Furthermore, the results of the current study are in line with the JIA costs reported in other studies. In a study by Prince et al. (2011), it was found that the mean annual costs of etanercept treatment in JIA patients in the Netherlands are around €12,478 [36]. Another study, performed by Kuhlman et al. (2016), reported annual direct healthcare costs of €14,648 in paediatric JIA patients in Germany [34]. A study conducted in the United Kingdom by Angelis et al. (2016) showed that the mean annual direct healthcare costs are €10,590 for adolescent JIA patients [35]. These three annual costs are slightly higher than the results of the current study, which is most likely explained by the fact that all patients in the current study were clinically inactive, while the other studies did not specifically target patients who were clinically inactive. A study by Minden et al. (2004) illustrates that disease state does influence annual costs, as they found that the average annual costs more than double when the disease was in an active state versus an inactive disease state [37].

On the other hand, there are also studies which report lower mean annual costs than in the current study. However, these are studies in which not all patients received bDMARDs treatment. To illustrate this, a study by Minden et al. (2009) found that the mean annual costs of JIA care were €4,663 per patient, both including direct and indirect healthcare costs [13]. However, patients who received bDMARDs incurred a mean annual treatment cost of €27,771, whereas the mean annual costs associated with non-bDMARD treatment were on average €3,155 per year. In addition, a study by Kip et al. (2021), in which all JIA patients were included, regardless of medication use and disease state, showed mean annual hospital-associated costs of €3,784 per patient [24]. Moreover, the study by Kip et al. (2021) concluded that the first year of treatment after JIA diagnosis is the most expensive, due to frequent contact with the rheumatologist and extensive laboratory testing and radiology investigations [24]. In the current study 43% of the patients are within their first year of JIA treatment during the pre-withdrawal period. However, there is no significant difference found between the annual costs of the patients within their first year of treatment after JIA diagnosis and the other patients [U(n=24, n=32,)=312.00, z=-1.19, p=0.23]. This could be explained by the minor attribution of the rheumatology visits (12.3%), laboratory testing (2.0%) and radiology investigations (1.2%) to the total annual costs, due to the fact that the patients were clinically inactive, which reduces the frequency of rheumatology visits, laboratory testing and radiology investigations compared to patients with active disease.

Due to the impact of the above-stated aspects (i.e. disease status, medication use, and time elapsed since JIA diagnosis) on the total annual cost, caution is required when comparing the results of the current study and other studies. In addition, the country in which the study was conducted and the used costing methodology must be considered as this might influence the JIA-related care costs as well. For instance, the guidelines and treatment strategies for JIA differ per country. In the Netherlands, patients do not have a waiting period before starting JIA treatment, whereas in some other countries there is a waiting period [38], which might influence the

treatment efficiency and therefore the healthcare resource use and accompanying costs. Moreover, the unit care costs could be different in other countries. The generalisability of the results to other countries is therefore dependent on the similarities and differences in the treatment protocols and unit costs. In addition, the costs for JIA-related care as reported in other studies are dependent on the used costing methodology, given that for example not all studies include direct and indirect costs or included out-of-pocket costs.

Limitations

The current study was subject to some limitations regarding data availability, costs estimations, generalisability of results and the comparability of the subgroups (abrupt discontinuation vs. taper).

Available data

Costs could have been missed due to a lack of data. Data is missing regarding within-hospital physician visits, other than visits to the paediatric rheumatologist, as these data were only available up to 12 December 2018 and could therefore not be included in the current analysis. However, an extensive study by Kip et al. (2021) shows that other within-hospital physician visits costs account for approximately one third of all outpatient hospital visits costs [24]. Moreover, the number of rheumatology visits and telephone consultations are not significantly different between the periods (Table 1), implying contact with specialists does not contribute to the total cost differences between pre-withdrawal and post-withdrawal periods. In addition, data regarding care outside the Wilhelmina Children's Hospital could not be included in the current study, including both care within other hospitals (e.g. ophthalmologists visits and JIA related hospitalisations or emergency department visits) and non-hospital associated care (e.g. physiotherapist, psychological support, JIA-related general practitioner visits). The included patients live throughout the Netherlands, which makes it likely that patients may have received JIA-related care in other hospitals than the Wilhelmina Children's Hospital. This applies in particular to emergency care and care that does not have to be provided exclusively by a specialised paediatric rheumatology centre. It was therefore decided to exclusively include hospitalisations and procedures under anaesthesia which were directly related to JIA treatment, in order to keep the data available constant, regardless of the place of residence. To assess the impact of this choice on the costs, the analysis is performed for patients living <15 kilometers from the Wilhelmina Children's Hospital, assuming they received all JIA-related care within the Wilhelmina Children's Hospital. In this analysis, all JIA-related care was included, also hospitalisations and procedures under anaesthesia, which were not directly related to JIA treatment, and emergency department visits. This analysis did increase the mean annual costs within the pre-withdrawal period by 0.8%, as one patient visited the emergency department within the follow-up period, associated by €287.64 [22] and €128.73 for travel expenses, parking costs and labour productivity losses. For all missing data as stated in this paragraph, it is unlikely that it would change the conclusion, as medication costs contribute to 63.2%-82.1% of the total cost. However, the impact of JIA on total costs from a societal perspective is currently evaluated in a large multi-centre, international prospective collaborative study into management strategies for JIA, conducted in Canada and the Netherlands, named UCAN CAN-DU (https://www.ucancandu.com/) [39]. It is therefore recommended to compare the results of the current study with the results of this prospective study.

Costs estimations

Challenges in estimating the unit costs need to be considered. To start with, the parameter which has major impact on the total costs is medication. In the current study, the medication costs are based on the tariffs reported by the National Healthcare Institute and might not correspond with the actual contract prices between the pharmaceutical company and the Wilhelmina Children's Hospital. In addition, price fluctuations are not included in the analysis, but are important for bDMARDs as biosimilars have entered the market. However, the sensitivity analysis shows that all drug prices would have to decrease simultaneously by at least 94% to change the overall conclusions, which is highly unlikely. In addition, labour productivity costs are based on the assumption that one caregiver attended the patient during hospital visits and missed working hours as a result. It might be that two parents have attended the patient or that the caregiver is out of work, for which different hourly productivity costs apply. However, varying the labour productively costs per hour by $\pm$25% has minor influence on the total cost difference (i.e. 0.40% and 0.26% for the cost difference between the 1) pre-withdrawal period and 2a) first year post-withdrawal and 2b) second year post-withdrawal, respectively), as shown by the sensitivity analysis. Next to the productivity losses of caregivers, it is known that a chronic disease does influence the productivity of children in the present and the future [40]. However, these costs could not be captured in the current study. Additionally, the Dutch Healthcare Authority tariffs are used for procedures under anaesthesia, which is not in line with the recommendation to determine the reference price for procedures under anaesthesia based on own cost price research, as stated in the Dutch Costing Manual [22]. However, the sensitivity analysis revealed that costs of procedures under anaesthesia only have a very minor impact on the total costs, making a bottom-up costing approach for costs of procedures under anaesthesia unnecessary.

Single-centre study

The current study is a single-centre study, which involves the lack of generalisability of study findings, however, as this study was conducted in the largest paediatric rheumatology treatment centre in the Netherlands, the results are expected to be highly representative of current practice.

Subgroup analysis

The two subgroups (i.e. abrupt discontinuation vs. taper) differ significantly in certain aspects. Therefore, it might be questionable whether it is fair to compare the two subgroups. For example, the taper subgroup is significantly older during the follow-period of this study ($p<0.05$), implying that these older children are, on average, heavier than younger children, and therefore receive higher doses bDMARDs, which entails higher costs. Another factor which could have influenced the results is the JIA subtype distribution. A previous study by Kip et al. (2021) showed that mean annual costs for bDMARDs are the lowest for persistent oligoarticular JIA, and the highest for RF-positive polyarticular JIA [16]. The taper subgroup relatively has a higher proportion of persistent oligoarticular JIA and a relatively lower proportion of RF-positive polyarticular JIA, Appendix C, Table 3. On the other hand, the two subgroups are similar in other aspects, such as gender and ANA status. Moreover, the two subgroups do not differ significantly in the median time to reach clinically inactive disease after starting bDMARD treatment [$U(n=25, n=30)=354.00$, $z=-0.59$, $p=0.55$] and in the median time to start TNF-α bDMARD withdrawal after reaching clinically inactive disease [$U(n=25, n=30)=364.50$, $z=-0.42$, $p=0.68$]. Despite the importance of the comparability of the subgroups and above stated differences, the costs of the subgroups are not significantly different within the pre-withdrawal period, indicating that it is

reasonable to compare costs between the two groups.

Implications for further research

The ultimate goal of JIA treatment is to reduce the patient's symptoms, restore their physical and psychological functioning, and thereby prevent or limit long-term joint damage and disability [10, 11]. Part of this treatment might be the withdrawal of bDMARDs after clinically inactive disease is reached. Until now, this decision was partly driven by the high costs of bDMARDs, but evidence into the costs of bDMARD withdrawal was still lacking. To create a complete picture of bDMARD withdrawal, additional studies are needed. First, further work is needed to fully understand the implications of withdrawal bDMARDs on the treatment effectiveness and the quality of life of patients. A study on the quality of life during withdrawal bDMARDs for rheumatoid arthritis in adults shows that withdrawal of bDMARDs is cost-saving, but decreases the quality of life compared to standard care [41]. The influence of withdrawal bDMARDs on quality of life in JIA patients is currently investigated in the UCAN CAN-DU project (https://www.ucancandu.com/) [39]. Second, to improve the generalisability of this study, a more extensive costing study is recommended which also incorporates non-TNF-α bDMARDs and other paediatric rheumatology treatment centres. Moreover, this will increase the number of included patients, which strengthens the findings. Finally, the study focused on two years after starting TNF-α bDMARD withdrawal. As the results indicate, costs increase in the second year compared to the first year post-withdrawal, due to the restart of bDMARDs and intensifying bDMARDs use. A further study investigating the long-term cost impact of bDMARD withdrawal is therefore recommended.

Conclusion

In summary, the results of the current study indicate that withdrawing TNF-α bDMARDs in JIA patients <18, in clinically inactive disease on TNF-α bDMARDs, significantly reduces the mean annual costs within the first and second year after starting TNF-α bDMARDs withdrawal compared to the period before starting TNF-α bDMARDs withdrawal. Medication costs were found to be the main cost driver in all periods and for all patients, regardless of the withdrawal strategy. The results imply that it is financially recommended to withdraw TNF-α bDMARD, in JIA patients after they reached clinically inactive disease on TNF-α bDMARDs, within the two years after starting TNF-α bDMARD withdrawal. The greatest cost reductions are achieved within the first year after starting TNF-α bDMARDs withdrawal. The second aim of the study was to compare the withdrawal strategies (abrupt discontinuation vs. taper). The cost differences between the 1) pre-withdrawal period and 2a) first year post-withdrawal and 2b) second year post-withdrawal do not differ significantly between the withdrawal strategies.

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Appendix A - Inclusion hospital-associated resource use and corresponding costs

For the analysis, hospital-associated resource use (including medication use) of the patient within the follow-up period of the patient is included. All costs were corrected for the inflation using the Consumer Price Indices (CPI) from Statistics Netherlands and the following formula:

$$Costs_{1January2022} = \frac{Costs_{YearSource}}{CPI_{YearSource}} \cdot CPI_{Year2021} \quad (1)$$

Radiology investigations

Radiology investigations with the status 'Completed', as recorded in the Research Data Platform, were included in the analysis. The costs were derived from a study by Kip et al. (2021) [16], and were set to zero if:

- The investigation was performed for (clinical) study purposes.
- The costs of the investigation were already included in another procedure performed on the same day.
- The investigation was judged to be unrelated to JIA by a paediatric rheumatologist.

The included radiology investigations and their frequencies were given in Figure 6.

Laboratory testing

Laboratory tests with the status 'Completed', as recorded in the Research Data Platform, were included in the analysis. The costs were derived from a study by Kip et al. (2021) [16], and were set to zero if:

- The test was already included in another investigation that day, such as Mean Platelet Volume, which reported for free when a thrombocyte count is performed.
- The test was conducted for clinical studies.
- The test that were clearly unrelated to JIA, such as a codfish allergy test.

The included laboratory tests and their frequency were given in Figure 7.

Rheumatology visits and telephone consultations

Only hospital visits to and telephone consultations with the department of Paediatric Rheumatology and with the status 'Completed', as recorded in the Research Data Platform, were included in the analysis. The following choices were made:

- Rheumatology visit with the label 'operational' were manually checked in the Electronic Medical Record to determine which activity has been conducted and if additional costs should be added.
- Appointments which were not labelled as telephone or in-person were assumed to be in-person.

The type of the included visits and their frequencies were given in Figure 8. The costs for rheumatology visits were based on the reference prices for outpatient visits at the paediatric department, as reported in the Dutch Costing Manual and additional costs were added for travel expenses, parking costs and labour productivity losses [22].

Hospitalisation

For hospitalisations, it was decided on an individual patient-level by a paediatric rheumatologist whether the visit was direct related to JIA care. Included hospitalisations were: bDMARD intravenous administration and hospitalisation after an intra-articular injection under sedation. The corresponding costs were determined using the reference prices for inpatient days at the paediatric department, as documented by the Dutch Costing Manual, plus additional costs for travel expenses, parking costs and labour productivity losses. For the bDMARD injection, the reference price as reported by the Dutch Healthcare Authority was used [23].

Procedures under anaesthesia

For procedures under anaesthesia, it was decided on an individual patient-level by a paediatric rheumatologist whether the visit was direct related to JIA care. Ultimately, only intra-articular injections under sedation were included within the follow-up period. The costs for this procedure were based on the tariffs of the Dutch Healthcare authority (€229.51) plus additional costs for travel expenses, parking costs and labour productivity losses. If a procedure under anaesthesia is accompanied by an day-care hospitalisation, the labour productivity losses costs, travel expenses and parking costs were charged once.

The number of intra-articular injections were determined using the operating room data file and an additional data file, in which the administration of the articular injections were separately reported. The intra-articular injections per patient within the follow-up period were excluded if the date of administration was equal to:

- the date of a intra-articular injection in the operating room to prevent double-counting. The costs for intra-articular steroid injections were are included as costs of 'Procedures under anaesthesia'.
- the date of a hospitalisation to prevent double-counting. The costs for intra-articular steroid injections were included in the hospitalisation costs category.

Medication

Medication use were manually extracted from the Electronic Medical Record. The following medicines were included in the analysis:

- abatacept
- adalimumab
- anakinra
- azathioprine
- baricitinib
- canakinumab
- cellcept (mycophenolic acid)
- certolizumab
- ciclosporin
- colchicine
- cyclophosfamide
- dexamethasone
- etanercept
- golimumab
- hydrocortisone
- hydroxychloroquine
- infliximab
- leflunomide
- methotrexate
- prednisolone

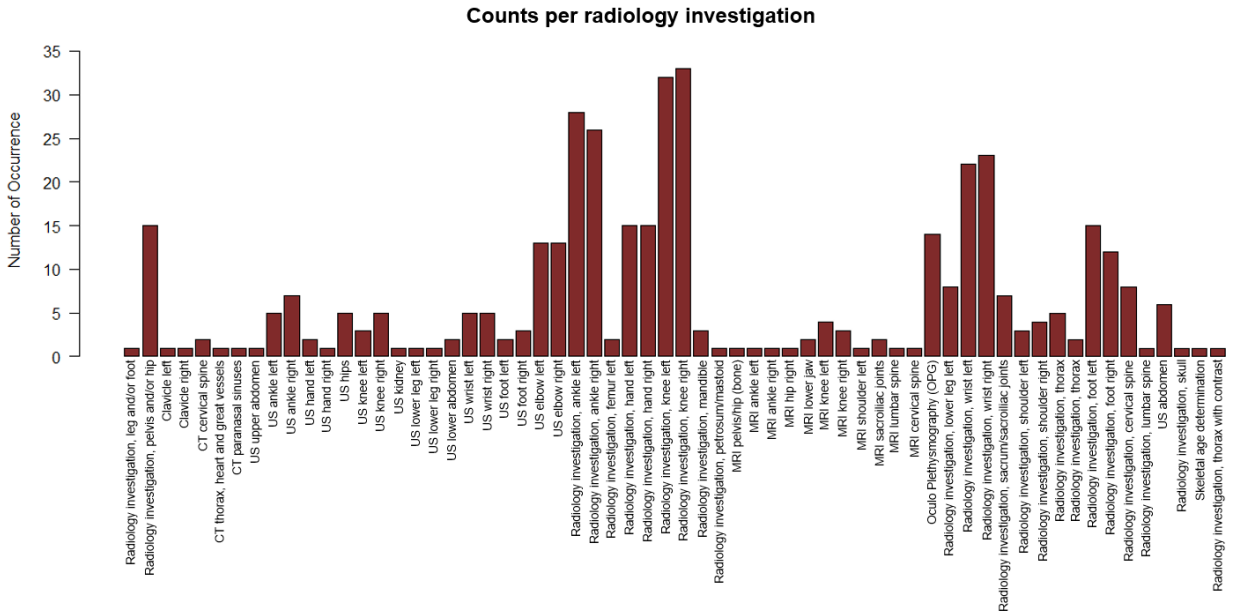

Figure 6. The counts per included radiology investigation during the follow-up period.

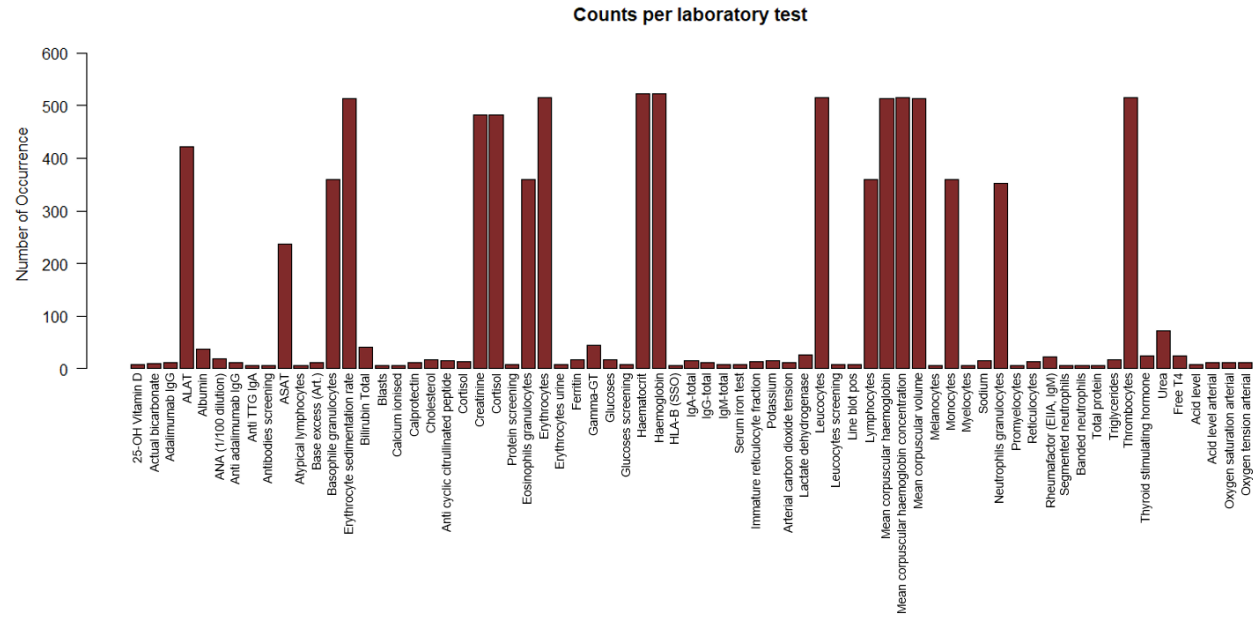

Figure 7. The counts per included laboratory tests during the follow-up period.

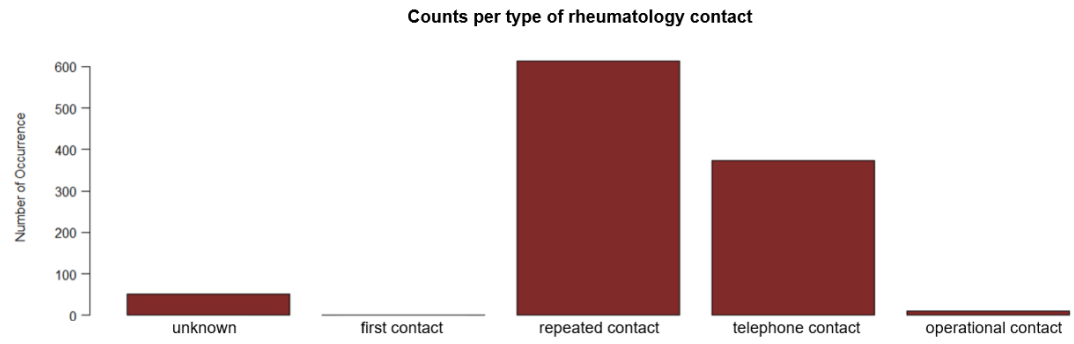

Figure 8. The counts per appointment type during the follow-up period. Operational contact means that an additional activity took place, for example medication administration during the rheumatology visit.

- rituximab
- sulfasalazine (salazopyrin)
- sarilumab
- secukinumab
- tocilizumab
- tofacitinib
- ustekinumab

All the dose changes or medicine changes were reported. The medicine names as stated above were matched to their pharmaceutical medicine name which is dispensed by the pharmacy to calculate the exact costs of the dispensed medicine. The costs were calculated using the following formula:

$$Costs_{Medication} = \left\lceil \frac{Date_{Stop} - Date_{Start}}{Interval_{days}} \right\rceil^{*} \cdot Costs_{Medication} + Costs_{Dispensing} \quad (2)$$

*The number of administrations is rounded up to avoid underestimation.
The dispensing costs were charged when the patient switches to another medicine/type/dose and were repeated every ninety days.

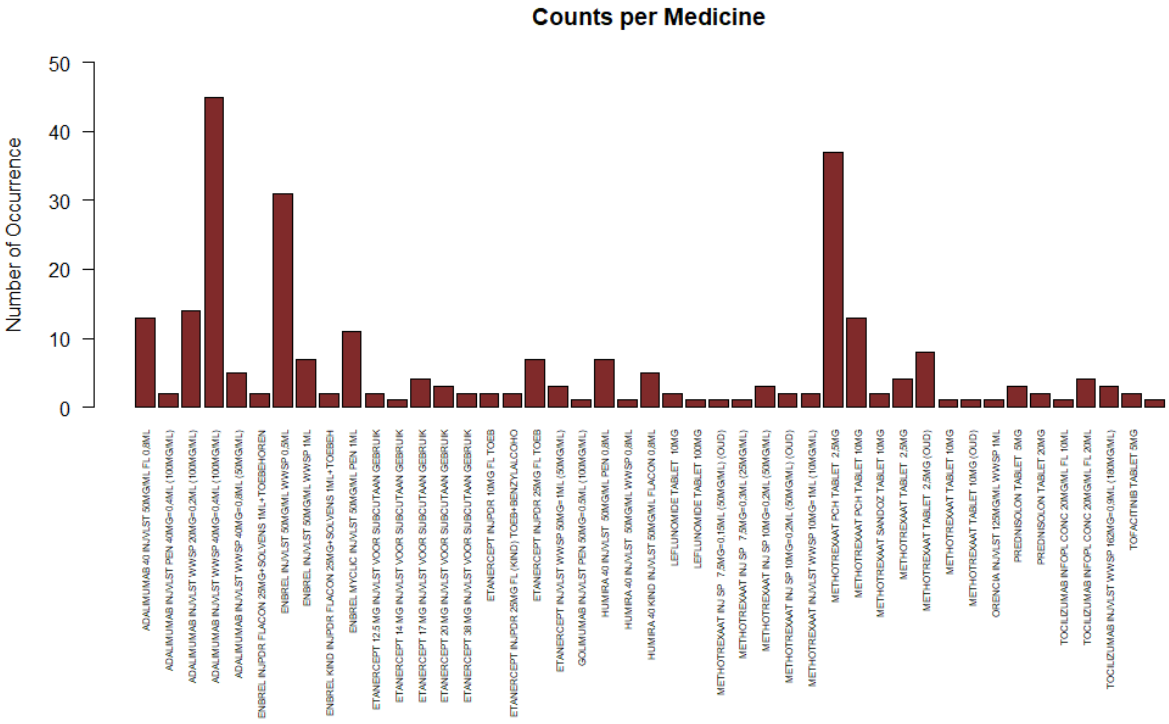

Figure 9. The counts per medicine during the follow-up period.

Appendix B - Costs of DMARDs

Table 2. Costs of DMARDs

DMARD	Name pharmaceutic file	Costs	Range
Abatacept [42]	ORENCIA INJVLST 125MG/ML WWSP 1ML	€270.89	
Adalimumab [43]	ADALIMUMAB 40 INJVLST 50MG/ML FL 0,8ML	€328.05	(€325.60 - €328.87)
	ADALIMUMAB INJVLST WWSP 20MG=0,2ML (100MG/ML)	€237.42	
	ADALIMUMAB INJVLST WWSP 40MG=0,4ML (100MG/ML)	€367.76	(€ 354.01 - €381.51)
	ADALIMUMAB INJVLST WWSP 40MG=0,8ML (50MG/ML)	€328.05	(€325.60 - €328.87)
	ADALIMUMAB INJVLST PEN 40MG=0,4ML (100MG/ML)	€367.76	(€354.01 - €381.51)
	HUMIRA 40 INJVLST 50MG/ML PEN 0,8ML	€328.05	(€325.60 - €328.87)
	HUMIRA 40 KIND INJVLST 50MG/ML FLACON 0,8ML	€328.05	(€325.60 - €328.87)
	HUMIRA 40 INJVLST 50MG/ML WWSP 0,8ML	€328.05	(€325.60 - €328.87)
Etanercept [44]	ENBREL INJPDR FLACON 25MG+SOLVENS 1ML+TOEBEHOREN	€94.67	
	ENBREL INJVLST 50MG/ML WWSP 0,5ML	€91.05	
	ENBREL INJVLST 50MG/ML WWSP 1ML	€165.91	
	ENBREL KIND INJPDR FLACON 25MG+SOLVENS 1ML+TOEBEH	€94.67	
	ETANERCEPT INJVLST WWSP 50MG=1ML (50MG/ML)	€172.68	
	ENBREL MYCLIC INJVLST 50MG/ML PEN 1ML	€165.91	
	ETANERCEPT 12.5 MG INJVLST VOOR SUBCUTAAN GEBRUIK	€65.29	
	ETANERCEPT 14 MG INJVLST VOOR SUBCUTAAN GEBRUIK	€73.12	
	ETANERCEPT 17 MG INJVLST VOOR SUBCUTAAN GEBRUIK	€88.79	
	ETANERCEPT 20 MG INJVLST VOOR SUBCUTAAN GEBRUIK	€104.46	
	ETANERCEPT 38 MG INJVLST VOOR SUBCUTAAN GEBRUIK	€198.47	
	ETANERCEPT 40 MG INJVLST VOOR SUBCUTAAN GEBRUIK	€208.92	
	ETANERCEPT INJPDR 10MG FL TOEB	€50.30	
	ETANERCEPT INJPDR 25MG FL TOEB	€94.67	
	ETANERCEPT INJPDR 25MG FL (KIND) TOEB+BENZYLALCOHO	€94.67	
Golimumab [45]	GOLIMUMAB 50 INJVLST 100MG/ML WWSP 0,5ML	€993.58	
	GOLIMUMAB INJVLST PEN 50MG=0.5ML (100MG/ML)	€993.58	
Leflunomide [46]	LEFLUNOMIDE TABLET 10MG	€1.87	(€1.33 - €2.41)
Methotrexate [47]	METHOTREXAAT INJ SP 7,5MG=0,3ML (25MG/ML)	€10.29	
	METHOTREXAAT INJ PEN 7,5MG=0,15ML (50MG/ML)	€14.81	
	METHOTREXAAT INJ SP 7,5MG=0,15ML (50MG/ML) (OUD)	€8.23	(€6.17 - €10.29)
	METHOTREXAAT INJ SP 10MG=0,2ML (50MG/ML)	€10.98	(€8.23 - €13.72)
	METHOTREXAAT INJ SP 10MG=0,2ML (50MG/ML) (OUD)	€10.98	(€8.23 - €13.72)
	METHOTREXAAT INJVLST WWSP 10MG=1ML (10MG/ML)	€10.98	(€8.23 - €13.72)
	METHOTREXAAT INJVLST WWSP 15MG=1,5ML (10MG/ML)	16.47	(€12.35 - €20.59)
	METHOTREXAAT PCH TABLET 2,5MG	€0.17	
	METHOTREXAAT PCH TABLET 10MG	€0.80	
	METHOTREXAAT SANDOZ TABLET 10MG	€0.80	
	METHOTREXAAT TABLET 2,5MG	€0.17	
	METHOTREXAAT TABLET 2,5MG (OUD)	€0.17	
	METHOTREXAAT TABLET 10MG	€0.80	
	METHOTREXAAT TABLET 10MG (OUD)	€0.80	
Tofacitinib [48]	TOFACITINIB TABLET 5MG	€13.51	
Tocilizumab [49]	TOCILIZUMAB INFOPL CONC 20MG/ML FL 10ML	€ 358.34	
	TOCILIZUMAB INFOPL CONC 20MG/ML FL 20ML	€ 716.68	
	TOCILIZUMAB INJVLST WWSP 162MG=0,9ML (180MG/ML)	€256.55	

Appendix C

Table 3. Characteristics of the patient population

Characteristics	Total (n=56)[1]	Abrupt discontinuation (n=26) [1]	Taper (n=30)[1]	Significance
Age at JIA diagnosis	7.5 (3.9-11.5)	5.9 (3.7-8.4)	10.4 (4.6-12.8)	U(n=25, n=30)=264.00, z=-2.07, **p<0.05**
Age at CID	10.2 (6.5-13.0)	7.6 (5.4-9.9)	12.1 (9.5-14.6)	U(n=25, n=30)=186.00, z=-3.35, **p<0.05**
Age at starting to withdrawal	11.1 (8.6-14.5)	8.9 (6.7-10.7)	13.4 (11.0-15.5)	U(n=25, n=30)=184.00, z=-3.38, **p<0.05**
Time JIA diagnosis to CID	13.4 (8.3-35.4)	13.2 (7.5-26.1)	13.4 (8.6-44.6)	U(n=25, n=30)=342.50, z=-0.78, p=0.44
Time start bDMARD to CID	5.4 (3.1-10.0)	5.2 (3.0-8.5)	5.4 (3.3-10.0)	U(n=25, n=30)=354.00, z=-0.59, p=0.55
Time CID to starting to withdrawal	12.2 (10.1-17.0)	12.5 (10.3-16.7)	12.0 (9.9-16.7)	U(n=25, n=30)=364.50, z=-0.42, p=0.68
Gender				two-tailed p_{fisher}=0.43
Female	31 (55%)	16 (62%)	15 (50%)	
Male	25 (45%)	10 (38%)	15 (50%)	
JIA subtype [2]				
Enthesitis-Related Arthritis	7 (12%)	1 (3.8%)	6 (20%)	two-tailed p_{fisher}=0.11
Extended Oligoarticular JIA	9 (16%)	4 (15%)	5 (17%)	two-tailed p_{fisher}=1.00
Persistent Oligoarticular JIA	15 (27%)	4 (15%)	11 (37%)	two-tailed p_{fisher}=0.13
Psoriatic Arthritis	5 (8.9%)	3 (12%)	2 (6.7%)	two-tailed p_{fisher}=0.65
RF-negative Polyarticular JIA	16 (29%)	11 (42%)	5 (17%)	**two-tailed p_{fisher}=0.04**
RF-positive Polyarticular JIA	4 (7.1%)	3 (12%)	1 (3.3%)	two-tailed p_{fisher}=0.33
ANA status [3]				two-tailed p_{fisher}=0.79
Positive	25 (45%)	11 (42%)	14 (47%)	
Negative	30 (54%)	15 (58%)	15 (50%)	
Missing	1 (1.8%)	0 (0%)	1 (3.3%)	
RF status [4]				two-tailed p_{fisher}=1.00
Positive	5 (8.9%)	3 (12%)	2 (6.7%)	
Negative	40 (71%)	21 (81%)	19 (63%)	
Missing	11 (20%)	2 (7.7%)	9 (30%)	
HLA B27 status [5]				two-tailed p_{fisher}=0.09
Positive	13 (23%)	4 (15%)	9 (30%)	
Negative	24 (43%)	15 (58%)	9 (30%)	
Missing	19 (34%)	7 (27%)	12 (40%)	

[1] Ages are reported in years and times in months as Median (Interquartile range), other characteristics as n (%), [2] JIA subtypes are based on the classification method by The International League of Associations for Rheumatology [50], [3] ANA= antinuclear antibody, [4] RF=Rheuma factor, [5] HLA B27= Human leukocyte antigen, which is a risk-factor for auto-immune diseases [51].

Appendix D

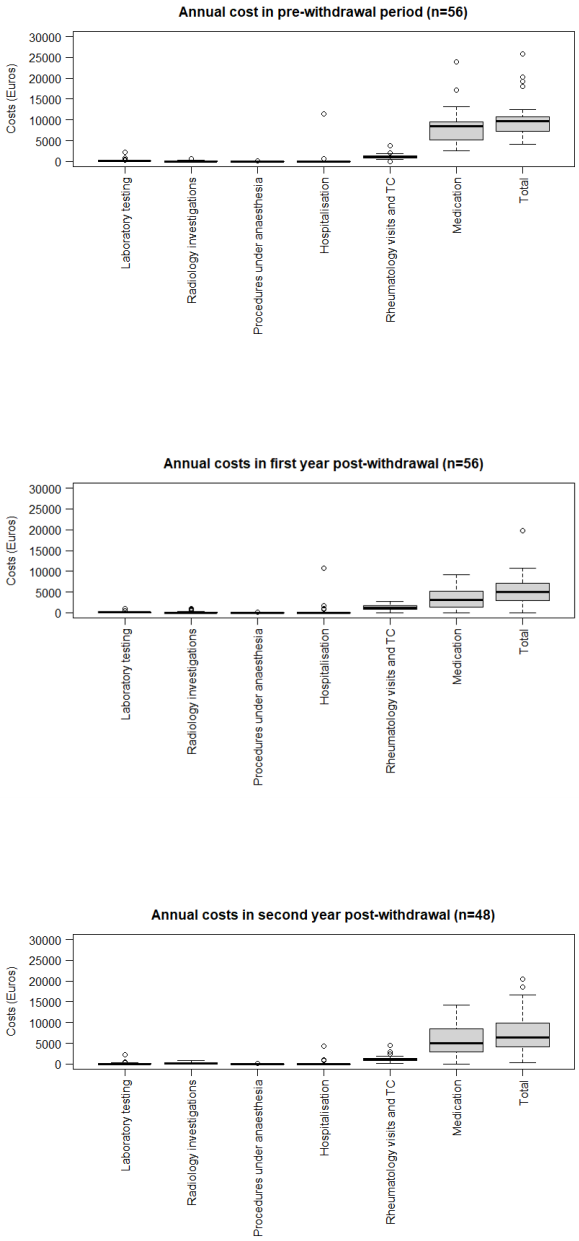

Figure 10. Annual costs in the second year post-withdrawal per category, TC= telephone consultation. Upper figure) pre-withdrawal period, Middle figure) first year post-withdrawal, Lower figure) second year post-withdrawal.

Table 4. Overview of the annual costs from a hospital perspective (reported as mean (95% confidence intervals)) given per group (total, abrupt discontinuation and taper), period (pre-withdrawal, first year post-withdrawal and second year post-withdrawal) and category (total, medication, rheumatology visits and telephone consultations, radiology investigations, laboratory testing, hospitalisations, and procedures under anaesthesia).

Group	Total			Abrupt discontinuation			Taper		
Category \ Period	pre-withdrawal (n=56)	1st post-withdrawal (n=56)	2nd post-withdrawal (n=48)	pre-withdrawal (n=56)	1st post-withdrawal (n=56)	2nd post-withdrawal (n=48)	pre-withdrawal (n=56)	1st post-withdrawal (n=56)	2nd post-withdrawal (n=48)
Total	**€9,138** (€8,210-€10,066)	**€4,492** (€3,716-€5,269)	€6,467 (€5,285-€7,649)	€9,027 (€7,352-€10,703)	€3,302 (€2,329-€4,275)	€6,275 (€4,566-€7,984)	€9,234 (€8,291-€10,176)	€5,524 (€4,477-€6,571)	€6,644 (€5,011-€8,276)
Medication	€8,090 (€7,215-€8,965)	€3,355 (€2,719-€3,990)	€5,498 (€4,395- €6,600)	€7,929 (€6,263-€9,594)	€2,211 (€1,331-€3,092)	€5,318 (€3,612-€7,024)	€8,230 (€7,468-€8,991)	€4,345 (€3,601-€5,090)	€5,663 (€4,426-€7,080)
Rheumatology visits & TC	€555 (€500-€610)	€610 (€542-€677)	€529 (€452-€606)	€653 (€560-€746)	€647 (€547-€747)	€485 (€397-€574)	€470 (€424-€516)	€578 (€488-€668)	€569 (€447-€690)
Radiology investigations	€122 (€79-€165)	€159 (€92-€226)	€185 (€125-€245)	€165 (€97-€234)	€196 (€97-€294)	€206 (€111-€301)	€85 (€34-€135)	€127 (€37-€216)	€166 (€91-€241)
Laboratory testing	€195 (€116-€274)	€145 (€104-€187)	€161 (€71-€250)	€236 (€80-€392)	€168 (€90-€246)	€192 (€14-€369)	€159 (€104-€214)	€126 (€90-€161)	€132 (€80-€185)
Hospitalisation	€174 (€0-€471)	€216 (€0-€495)	€90 (€0-€212)	€45 (€0-€104)	€80 (€0-€166)	€64 (€0-€149)	€286 (€0-€836)	€333 (€0-€845)	€114 (€0-€334)
Procedures under anaesthesia	€2 (€0-€7)	€8 (€0-€19)	€5 (€0-€14)	€0 (€0-€0)	€0 (€0-€0)	€10 (€0-€29)	€4 (€0-€13)	€15 (€0-€36)	€0 (€0-€0)

TC=Telephone Consultation

Appendix E

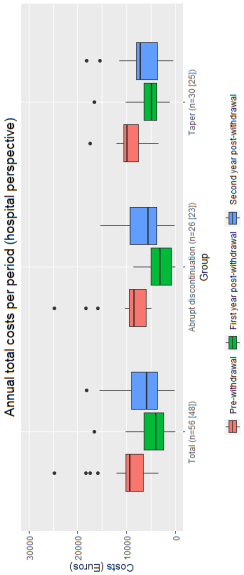

Figure 11. The annual total costs based on a hospital perspective per period (pre-withdrawal, first year post-withdrawal, and second year post-withdrawal) for the total group, discontinuation group and taper group. The number in brackets represents the number of patients included in the pre-withdrawal period and first year post-withdrawal. The number in the squared brackets represents the patients included in the second year post-withdrawal.

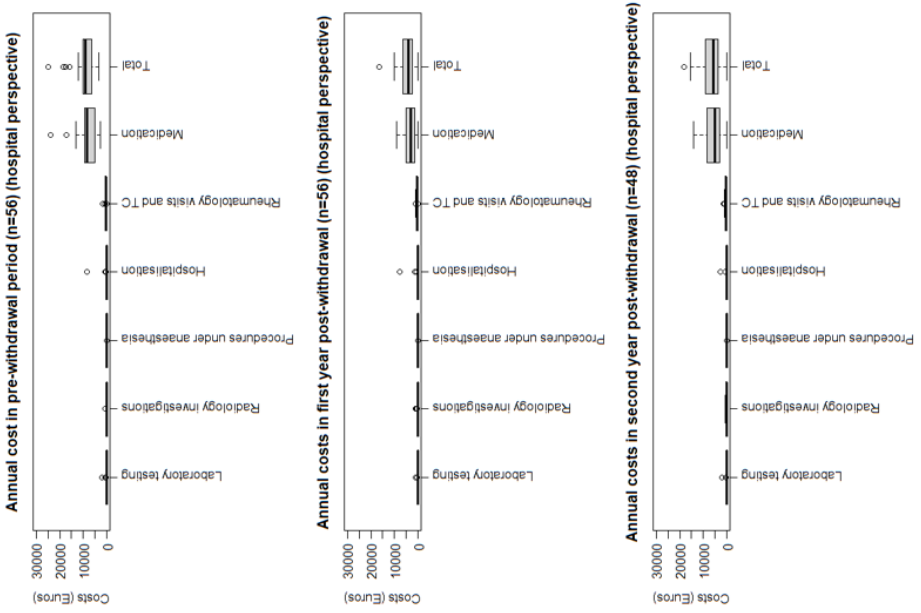

Figure 12. Annual costs based on a hospital perspective in the three periods per category, TC= telephone consultation. Upper figure) pre-withdrawal period, Middle figure) first year post-withdrawal, Lower figure) second year post-withdrawal.