UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Clínica Universitária de Reumatologia

Impact of oral versus subcutaneous methotrexate treatment on the quality of life of children with Juvenile Idiopathic Arthritis

Madalena da Silva Couto

Orientado por:

Professora Doutora Maria José Santos

Co-Orientado por:

Doutora Sandra Nunes Sousa

MAIO'2022

“Para ser grande, sê inteiro: nada teu exagera ou exclui. Sê todo em cada coisa. Põe quanto és no mínimo que fazes. Assim em cada lago a lua toda brilha, porque alta vive.”

Ricardo Reis

Abstract

Methotrexate (MTX), administered either orally or subcutaneously, remains the mainstay of Juvenile Idiopathic Arthritis (JIA) treatment because of its effectiveness and acceptable safety profile.

No significant differences between the two routes of administration have been reported, but some studies demonstrated a greater bioavailability with subcutaneous route, especially with higher doses.

Nevertheless, fear of injections, among other concerns, can compromise the quality of life and medication adherence.

This project addresses the impact of orally and subcutaneously administered MTX on the quality of life of children and adolescents with JIA, as well as the effectiveness and side effects with both routes of administration. The database Reuma.pt was used to perform an observational study. The quality of life was measured by JAMAR and EQ-5D-Y questionnaires, and effectiveness assessed by the improvement in disease activity and function. Side effects that led to change of dose or route of administration or MTX discontinuation were also collected.

A total of 26 children and adolescents with JIA, 65.4% females, with a mean age of 11.9, a median age at diagnosis of 2.7 and a mean disease duration of 7.5 years were included. 17 treatment courses with subcutaneous and 29 with oral MTX were analyzed. The median scores of EQ-5D-Y were 0.85 and 1 ($p=0.864$) and of JAMAR for children were 4 and 3.5 ($p=0.818$), for subcutaneous and oral routes of administration, respectively. Regarding effectiveness, subcutaneous MTX was superior to oral MTX, in terms of JADAS and ESR reduction at 6 months and reduction of pain. However, the dosage of subcutaneous MTX was significantly higher. Both subcutaneous and oral MTX were well tolerated.

In this cohort, the route of administration of MTX did not affect quality of life. MTX was effective and well tolerated regardless of the route of administration.

Keywords: Juvenile Idiopathic Arthritis; Methotrexate; Quality of Life; Effectiveness; Adverse reactions

Resumo

O metotrexato (MTX) continua a ser a terapêutica de eleição na Artrite Idiopática Juvenil (AIJ), podendo ser administrado por via oral ou subcutânea. Não existem diferenças significativas entre as duas vias de administração, contudo, alguns estudos demonstraram uma maior biodisponibilidade e melhores respostas com o uso de MTX subcutâneo, sobretudo quando em doses mais elevadas. No entanto, um maior receio das injeções, entre outros, pode comprometer a qualidade de vida e a adesão à terapêutica.

Este projeto visa comparar o impacto do MTX oral versus subcutâneo na qualidade de vida de crianças e adolescentes com AIJ, bem como a efetividade e os efeitos adversos.

Com esse propósito realizou-se um estudo observacional de coorte, seguida prospectivamente no Reuma.pt. A qualidade de vida foi avaliada pelo JAMAR e EQ-5D-Y e a efetividade pela melhoria da atividade da doença e da função. Os efeitos adversos que levaram a alteração de dose, via de administração ou descontinuação foram recolhidos.

Um total de 26 crianças e adolescentes com AIJ, 65.4% raparigas, com uma idade média de 11.9, uma mediana de idade de diagnóstico de 2.7 e uma média de duração de doença de 7.5 anos, foram incluídos. Foram analisados 17 cursos terapêuticos com MTX subcutâneo e 29 com oral. As medianas do EQ-5D-Y foram 0.85 e 1 (p=0.864) e as medianas do JAMAR-criança foram 4 e 3.5 (p=818) para a via subcutânea e oral, respetivamente. O MTX subcutâneo foi superior ao oral na redução da dor, e do JADAS e VS aos 6 meses. Contudo, a dose de MTX subcutâneo foi superior. A tolerância foi semelhante entres as duas vias de administração.

Nesta coorte, a via de administração do MTX não afetou a qualidade de vida. O MTX foi eficaz e bem tolerado, independentemente da via de administração.

Palavras-chave: Artrite Idiopática Juvenil; Metotrexato; Qualidade de vida; Efetividade; Efeitos adversos

O Trabalho Final é da exclusiva responsabilidade do seu autor, não cabendo qualquer responsabilidade à FMUL pelos conteúdos nele apresentados.

Table of contents

Abbreviations and Acronyms

C-HAQ – Childhood Health Assessment Questionnaire

CRP – C-Reactive Protein

DMARD – Disease-modifying anti-rheumatic drug

- **bDMARD** – Biologic disease-modifying anti-rheumatic drug
- **csDMARD** – Conventional synthetic disease-modifying anti-rheumatic drug

ESR – Erythrocyte sedimentation rate

ILAR – International League of Associations of Rheumatology

IQR – Interquartile range

JADAS – Juvenile Arthritis Disease Activity Score

JAMAR – Juvenile Arthritis Multidimensional Assessment Report

JIA – Juvenile Idiopathic Arthritis

MTX – Methotrexate

NRS – Numerical rating scale

NSAIDs – Non-steroidal anti-inflammatory drugs

SC – Subcutaneous

VAS – Visual Analogic Scale

Introduction

Juvenile Idiopathic Arthritis (JIA) comprises a group of heterogenous rheumatic diseases – forms of arthritis of unknown etiology – characterized by persistent joint inflammation lasting for at least 6 weeks and with onset before the age of 16 years. JIA is the most common chronic rheumatic disease in childhood and an important cause of short and long-term disability (Giancane et al., 2016).

The International League of Associations of Rheumatology (ILAR) classifies JIA into seven mutually exclusive categories, based on their clinical and laboratory features present in the first 6 months of illness, namely systemic arthritis, oligoarticular arthritis (extended or persistent), polyarticular arthritis (rheumatoid factor positive and rheumatoid factor negative), psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. The subsets of JIA differ in their clinical presentation, disease course and treatment response (Ferrara et al., 2018; Giancane et al., 2016, Santos et al., 2016).

Oligoarticular arthritis affects 4 or fewer joints during the first 6 months of disease. Oligoarticular arthritis is the most common subtype of JIA and can be divided into two further subsets: persistent oligoarticular arthritis, if arthritis remains confined to 4 or fewer joints during the whole disease course, and extended oligoarticular arthritis, if arthritis involves 5 or mores joints after the initial 6 months of illness. Oligoarthritis affects predominantly female patients and has an early disease onset, usually before the age of 6 years. It manifests as an asymmetrical arthritis, with high frequency of positive ANA and high risk of uveitis.

Rheumatoid factor positive polyarticular arthritis (affects 5 or more joints) is the least common subtype of JIA (Giancane et al., 2016).

In systemic arthritis, systemic features can persist, or it can evolve to a polyarticular form of arthritis (Santos et al., 2016)

In the last decades, the therapeutic progress has significantly reduced the morbidity associated with JIA. However, treatments are not curative, and many children continue to have active disease that extends to adulthood. Early treatment is essential to limit disease progression and to induce remission (Crayne & Beukelman, 2018).

In polyarticular, extended oligoarticular JIA and in systemic arthritis with predominant articular inflammation, methotrexate (MTX) continues to be the treatment of choice because of its effectiveness at achieving disease control with acceptable side effects in children (Ferrara et al., 2018; Giancane et al., 2016; Ramanan & Whitworth, 2003).

MTX is generally initiated after failure of non-steroidal anti-inflammatory drugs and/or intra-articular corticosteroid injections. In patients with high disease burden and inflammatory activity, as well as worse prognostic factors, MTX should be used as the first line treatment (Santos et al., 2016). MTX can be administered orally or subcutaneously, and the choice between one or the other route of administration generates some controversy.

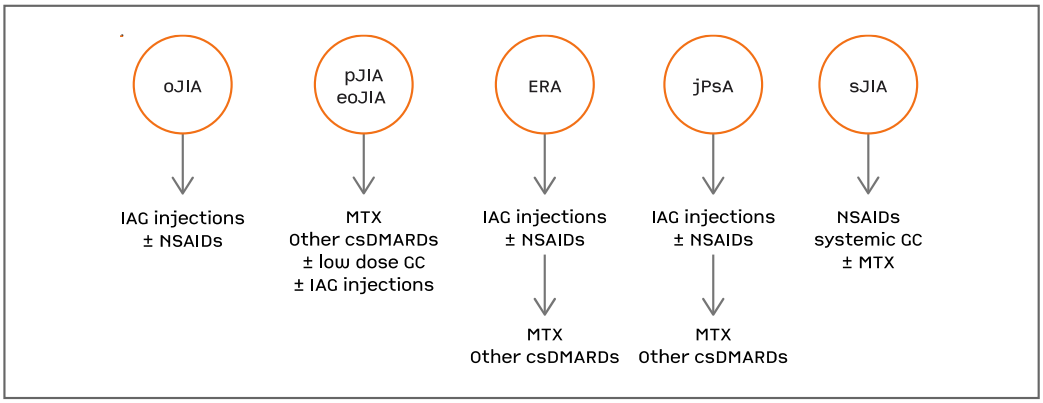

Figure 1: Conventional treatment according to JIA phenotype (Santos et al., 2016)

JIA – Juvenile Idiopathic Arthritis; oJIA – oligoarticular JIA; pJIA – polyarticular JIA; eoJIA – extended oJIA; ERA – enthesitis-related arthritis; jPsA – juvenile psoriatic arthritis; sJIA – systemic JIA; IAG – intra-articular glucocorticoids: GC – glucocorticoids; NSAIDs – non-steroidal anti-inflammatory drugs; MTX – methotrexate

Even though the effectiveness and safety profile of MTX are well known, less than half of patients remain on treatment two years after the beginning of MTX. The main reason for suspension of treatment is gastrointestinal adverse reactions (nausea, vomits, transaminase elevation) (Kearsley-Fleet et al., 2019).

According to the literature there are no significant differences, in terms of side effects, between the two routes of administration. Some studies demonstrated a greater

bioavailability and better responses to treatment with subcutaneous route, comparatively to oral route, especially with higher doses (Ferrara et al., 2018; Ramanan & Whitworth, 2003). Nevertheless, the concerns of parents with subcutaneous route of administration and fear of injections can compromise the quality of life and adherence to the medication (Mulligan et al., 2013).

Objectives

This project addresses the impact of orally administered and subcutaneously administered MTX on the quality of life of children and adolescents with JIA, as well as the effectiveness and side effects of both routes of administration.

Primary Objective

- Evaluate the quality of life of children with JIA under treatment with oral MTX and subcutaneous MTX

Secondary Objectives

- Evaluate the satisfaction with oral and subcutaneous routes of administration
- Evaluate school problems and troubles related to the medication reported by children and adolescents and their parents
- Evaluate the effectiveness of treatment with oral MTX and subcutaneous MTX
- Evaluate the safety profile of oral MTX and subcutaneous MTX

Methods

1. Patients

We used the database Reuma.pt to perform a cross-sectional, observational study. We included patients younger than 18 years of age diagnosed with Juvenile Idiopathic Arthritis, followed at Hospital Garcia de Orta and willing to participate.

All patients and respective families gave their informed consent for data collection and analysis.

2. Study variables

The quality of life was evaluated at last appointment using JAMAR and EQ-5D-Y questionnaires. Satisfaction with treatment was assessed on a numeric rating scale (NRS) and school problems reported by children and their parents, as well as troubles related to the medication, were also collected at last appointment. The effectiveness of MTX was assessed for each treatment course at 6 and 12 months.

Patients were classified as responders if achieving minimal disease activity according to JADAS definition for oligoarticular ($\leq$2) and for polyarticular ($\leq$3.8) JIA or showing an improvement of at least 50% in the number of active joints and did not start a biologic or receive systemic or intra-articular glucocorticoids. In case of MTX discontinuation before 6 or 12 months due to ineffectiveness or side effects, the participant was also considered as non-responder. Additionally, improvement in Juvenile Disease Activity Score (ΔJADAS) and its components, and in Childhood Health Assessment Questionnaire (ΔC-HAQ) were measured at 6 and 12 months.

Safety was assessed by side effects reported along the follow-up under MTX treatment that led to a change in dose, change in route of administration or drug discontinuation.

Information about activity of the disease (tender and swollen joints, VAS, ESR, CRP and JADAS), functional capacity (C-HAQ), dose and route of administration of MTX and

concomitant medication was collected at the time of MTX start and after 6 and 12 months.

Information about activity of the disease (tender and swollen joints, VAS, ESR, CRP and JADAS), functional capacity (C-HAQ), JAMAR, EQ-5D-Y, and satisfaction with medication on a NRS (0-10) was collected at last appointment.

3. Statistical Analysis

A descriptive analysis of patients under MTX treatment, administered orally or subcutaneously, was performed. Categorical variables were described using frequencies and percentages. Continuous variables were described using means and standard deviation or medians and interquartile range, according to the normality of distribution.

Route of administration of MTX was compared. Categorical variables were compared using the *chi-square test* or *Fisher's exact test* and continuous variables were compared using the *t-student test*, *Mann-Whitney test* or the *Kruskal-Wallis test*.

The relation between each route of administration of methotrexate and the quality of life was evaluated by the *Mann-Whitney test*.

A descriptive analysis of the adverse events reported during the follow-up under MTX treatment was performed, separately for each route of administration.

A descriptive analysis of school problems and troubles related to the medication was performed.

Each patient could contribute with more than one MTX treatment course to the analysis (eg switching from oral to subcutaneous administration).

4. Ethical considerations

This study protocol was approved by the Ethics Committee of Hospital Garcia de Orta.

Patients and parents provided written informed consent before inclusion. The research was carried out in accordance with the Declaration of Helsinki.

Results

- **Population characterization**

In total, 26 children and adolescents with JIA followed at Hospital Garcia de Orta were included, 17 girls (65.4%) and 9 boys (34.6%).

Demographic and clinical characteristics are summarized in Table 1.

Table 1 – Demographic and clinical characteristics of children and adolescents with JIA

Variables	N = 26	Oral N = 9	Subcutaneous N = 6
Gender, Female N (%)	17 (65.4)	4 (44.4)	5 (83.3)
Age (mean ± SD) *years*	11.9 ± 0.8	10.9 ± 1.7	12.2 ± 1.4
Disease duration (mean ± SD) *years*	7.5 ± 0.8	7.6 ± 1.4	10.8 ± 1.5
JIA ILAR category N (%)			
Persistent oligoarticular arthritis	8 (30.8)	3 (33.3)	2 (33.3)
Extended oligoarticular arthritis	8 (30.8)	2 (22.2)	4 (66.7)
RF + Polyarticular arthritis	0	0	0
RF − Polyarticular arthritis	3 (11.5)	1 (11.1)	0
Systemic arthritis	3 (11.5)	1 (11.1)	0
Psoriatic arthritis	2 (7.7)	1 (11.1)	0
Enthesitis-related arthritis	1 (3.8)	1 (11.1)	0
Undifferentiated arthritis	1 (3.8)	0	0
Last appointment (median, IQR)			
JADAS (N=21/N=8/N=6)	1.3 (4.9)	2 (7.3)	1 (5.3)
ESR mm/h/ CRP mg/dL (N=23/N=15)	11 (9)/0.06 (0.15)	11 (12)/0.06 (0.2)	8 (12)/0.06 (0.3)
Swollen/ tender joints (N=26/N=15)	0/0	0/0	0/0
Current DMARD therapy N (%)			
None	6 (23.1)	-	-
MTX with or without bDMARD	15 (57.6)	-	-
bDMARD monotherapy	5 (19.1)	-	-

DMARD – Disease-modifying antirheumatic drugs; bDMARD – Biologic disease-modifying antirheumatic drugs; JIA – Juvenile Idiopathic Arthritis; MTX – Methotrexate; RF – Rheumatoid Factor

The mean age at last appointment was 11.9 ± 0.8 years old and the median age at diagnosis was 2.7 (IQR 5.1) years old, a minimum of 0.7 and maximum of 16.9 years old.

At last appointment, the mean weight of the 26 patients was 43.4 ± 3.4 Kg, and the median height was 152.5 cm with an interquartile range of 34.3, a minimum of 108 cm and a maximum of 173 cm.

Twenty (77%) patients were under a csDMARD or bDMARD treatment: MTX alone or in combination with a bDMARD (N=15), or bDMARD monotherapy (N=5).

The treatment options at last appointment are summarized in Table 2.

Table 2 – Treatment at last appointment

Treatment N (%) Total = 26	None	6 (23.1)
	Oral MTX (± bDMARD)	9 (34.6)
	Subcutaneous MTX (± bDMARD)	6 (23)
	bDMARD monotherapy	5 (19.1)

bDMARD – Biologic disease-modifying antirheumatic drugs; MTX – Methotrexate

Of the 15 patients being treated with MTX, in 7 of them MTX was used in monotherapy (orally in 6 (23.1%) and subcutaneously in 1 (3.8%)). In 8 patients MTX was used in association with a bDMARD: subcutaneous MTX + adalimumab (11.5%), subcutaneous MTX + etanercept (7.7%) and oral MTX + adalimumab (11.5%). Finally, 5 patients (19.1%) were under bDMARD monotherapy: adalimumab (11.5%), etanercept (3.8%) and anakinra (3.8%).

Of the 6 patients (23.1%) who were not on any DMARD treatment: 4 had stopped DMARD (2 for being in remission, 1 for intolerance to MTX treatment and 1 for refusal);

and in 2 JIA has been controlled with NSAIDs and/or systemic or intra-articular corticosteroids.

- **Methotrexate treatment courses**

Some patients received more than one treatment course with MTX, either orally or subcutaneously. Some switched the route of administration from oral to subcutaneous administration or vice-versa, others have discontinued MTX treatment during a variable period and then reintroduced MTX treatment.

Therefore, this resulted in 46 treatment courses (Table 3). In 11 of them MTX was used in association with a bDMARD and in 1 of them MTX was used in association with Sulfasalazine (enthesitis-related arthritis). In 3 courses, MTX was used in combination with a glucocorticoid. In the remaining courses of treatment, MTX was used as monotherapy.

Table 3 – Methotrexate treatment courses

	MTX oral	MTX subcutaneous
Treatment courses N (%)	29 (63)	17 (37)

MTX – Methotrexate

As shown in Table 4, the mean dosage of subcutaneous MTX was significantly higher than the mean dosage of oral MTX (0.58 mg/Kg versus 0.45 mg/Kg, *p-value* = 0.008).

Table 4 – Methotrexate dose per kilogram of body weight

Dose/Weight (mg/Kg)	Subcutaneous (N=17)	Oral (N=26)	*p-value*
Mean ± SD	0.58 ± 0.031	0.45 ± 0.03	0.008
Min-Max	0.3 – 0.75	0.23 – 0.83	

- **Quality of Life in children and adolescents with JIA – overall and according to treatment**

Quality of life was evaluated using the EQ-5D-Y and JAMAR (Juvenile Arthritis Multidimensional Assessment Report) questionnaires. EQ-5D-Y questionnaire has 2 parts: a descriptive system and a *Visual Analogic Scale* (VAS). The descriptive system comprises five dimensions: mobility, looking after myself, doing usual activities, having pain or discomfort, and feeling worried, sad, or unhappy. Each dimension has three levels: no problems, some problems, and a lot of problems. The VAS records the patient evaluation of his health, from 0 to 100, 0 being "the worst health you can imagine" and 100 being "the best health you can imagine".

A final score from 0 to 1 was obtained, the closer to 1 the better the patient's rating of quality of life.

The JAMAR questionnaire has 10 questions about quality of life. These include 2 subdimensions: 5 questions on physical health and 5 questions on psychosocial health. The total score ranges from 0 to 30 and a separate score for each of the subscales ranges from 0 to 15. The higher the score, the worst the quality of life evaluation.

26 patients answered the EQ-5D-Y questionnaire, which results are listed in Tables 5 and 6 and in Figure 2. The median score was 0.88 (IQR 0.42) with a minimum score of 0.29 and a maximum score of 1.

Table 5 – EQ-5D-Y at last appointment: descriptive analysis

EQ-5D-Y	N=26
Median (IQR)	0.88 (0.42)

Table 6 – EQ-5D-Y dimensions at last appointment: descriptive analysis

EQ-5D-Y dimension	N = 26 (%)
Mobility	
No problems	20 (76.9)
Some problems	6 (23.1)
A lot of problems	0
Looking after myself	
No problems	25 (96.2)
Some problems	1 (3.8)
A lot of problems	0
Doing usual activities	
No problems	20 (76.9)
Some problems	6 (23.1)
A lot of problems	0
Having pain or disconfort	
No problems	14 (53.8)
Some problems	11 (42.3)
A lot of problems	1 (3.8)
Feeling worried, sad, or unhappy	
Not worried, sad, or unhappy	21 (80.8)
A bit worried, sad, or unhappy	5 (19.2)
Very worried, sad, or unhappy	0

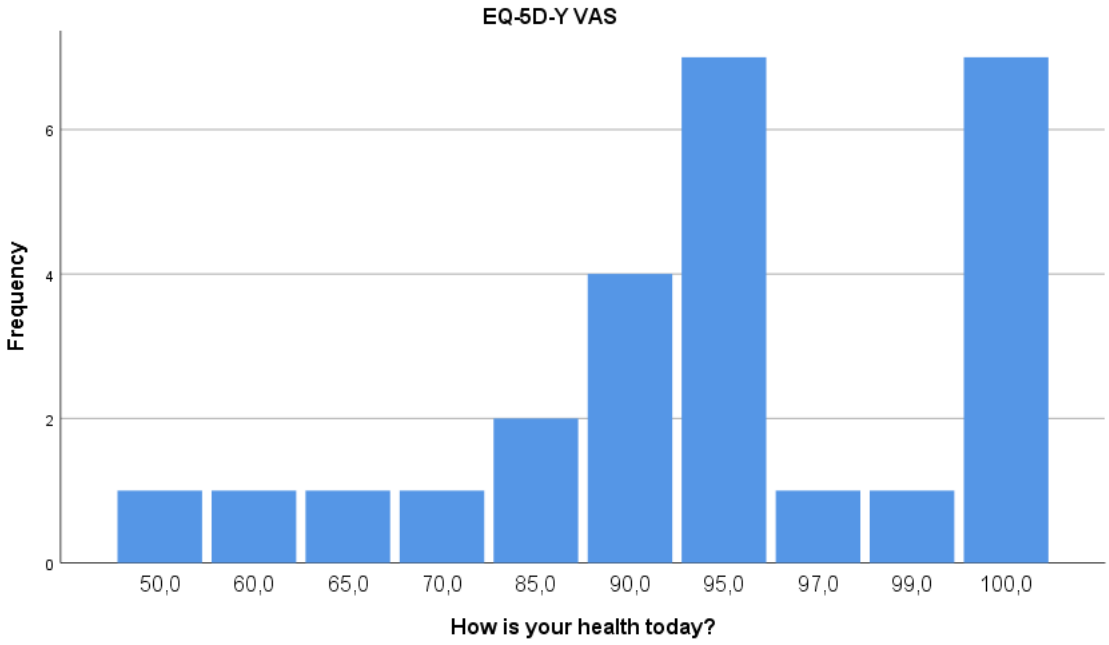

Figure 2 - EQ-5D-Y VAS at last appointment: descriptive analysis

22 children (4 children under 7 years old did not answer) and 25 parents answered the JAMAR questionnaire. The 10 questions about quality of life were analyzed.
Moreover, these children have rated their overall well-being on a 21-numbered circle VAS (0 corresponding to very well and 10 corresponding to very poorly).

The results are listed in Table 7.

Table 7 – JAMAR at last appointment: descriptive analysis

	JAMAR Children N=22			
	Total (0-30)	Physical (0-15)	Psychosocial (0-15)	VAS well-being (0-10)
Median value (IQR)	4 (7.25)	1 (4)	1.5 (3)	0.5 (2.1)
	JAMAR Parents N=25			
	Total (0-30)	Physical (0-15)	Psychosocial (0-15)	VAS well-being (0-10)
Median value (IQR)	1 (3.9)	1 (2)	1 (2)	0.5 (2)

JAMAR – Juvenile Arthritis Multidimensional Assessment Report; VAS – Visual Analogic Scale

In JAMAR for children, the median of the total score was 4 (IQR 7.25), with a minimum score of 0 and a maximum score of 10. The median of the physical subscale was 1 (IQR 4), with a minimum of 0 and a maximum of 7. The median of the psychosocial subscale was 1.5 (IQR 3), with a minimum of 0 and a maximum of 6.

In JAMAR for parents, the median of the total score was 1 (IQR 3.9), with a minimum score of 0 and a maximum score of 15. The median of the physical subscale was 1 (IQR 2), with a minimum of 0 and a maximum of 7. The median of the psychosocial subscale was 1 (IQR 2), with a minimum of 0 and a maximum of 8.

The median score of the 21-numbered circle VAS was 0.5 for both children and parents (IQR 2.1 and 2 respectively), with a minimum score of 0 and a maximum score of 6.5 for children and 7 for parents.

*

A comparison of the quality of life between oral and subcutaneous MTX treatment was made (N=15).

The results are presented in Table 8.

Table 8 – Quality of life: oral versus subcutaneous methotrexate

Variable	SC (N=6) *	Oral (N=9) *	*p-value*
EQ-5D-Y (N=15)	0.85	1	0.864
JAMAR total children (N=12)	4	3.5	0.818
JAMAR physical children (N=12)	2.5	1	0.937
JAMAR psychosocial children (N=12)	1	1	0.937
VAS well-being children (N=12)	0	0	0.818
JAMAR total parents (N=15)	1	0	0.456
JAMAR physical parents (N=15)	1	0	0.689
JAMAR psychosocial parents (N=15)	1	0	0.776
VAS well-being parents (N=15)	0.5	0	0.776

JAMAR – Juvenile Arthritis Multidimensional Assessment Report; VAS – Visual Analogic Scale
*median value

A comparison between the quality of life's results for each of the 4 group of patients, summarized previously, was made.

The results are presented in Table 9.

Table 9 – Quality of life: comparison of the 4 therapeutic groups

Variable	None *	Oral *	SC *	bDMARD *	*p-value*
	N=6	N=9	N=6	N=5	
EQ-5D-Y (N=26)	0.64	1	0.85	1	0.153
JAMAR total children (N=22)	3.5	3.5	4	3	0.979
JAMAR physical children (N=22)	0.5	1	2.5	0.5	0.941
JAMAR psychosocial children (N=22)	2	1	1	2	0.881
VAS well-being children (N=22)	2.8	0	0	0.8	0.308
JAMAR total parents (N=25)	2	0	1	2	0.622
JAMAR physical parents (N=25)	1	0	1	1	0.789
JAMAR psychosocial parents (N=25)	1	0	1	1	0.696
VAS well-being parents (N=25)	1.5	0	0.5	0.5	0.928

JAMAR – Juvenile Arthritis Multidimensional Assessment Report; SC – Subcutaneous; VAS – Visual Analogic Scale
*median value

There are no statistically significant differences on the quality of life between treatment groups: oral MTX, subcutaneous MTX, bDMARD, and no DMARD (*p-value* > 0.05).

- **Therapeutic Satisfaction**

JIA patients on DMARD treatment at last appointment classified their satisfaction with treatment in a numerical rating scale (NRS), from 0 to 10, 10 corresponding to very happy.

Results are presented in Figure 3.

The median score was 10 (IQR 1) with a minimum score of 5 and a maximum score of 10.

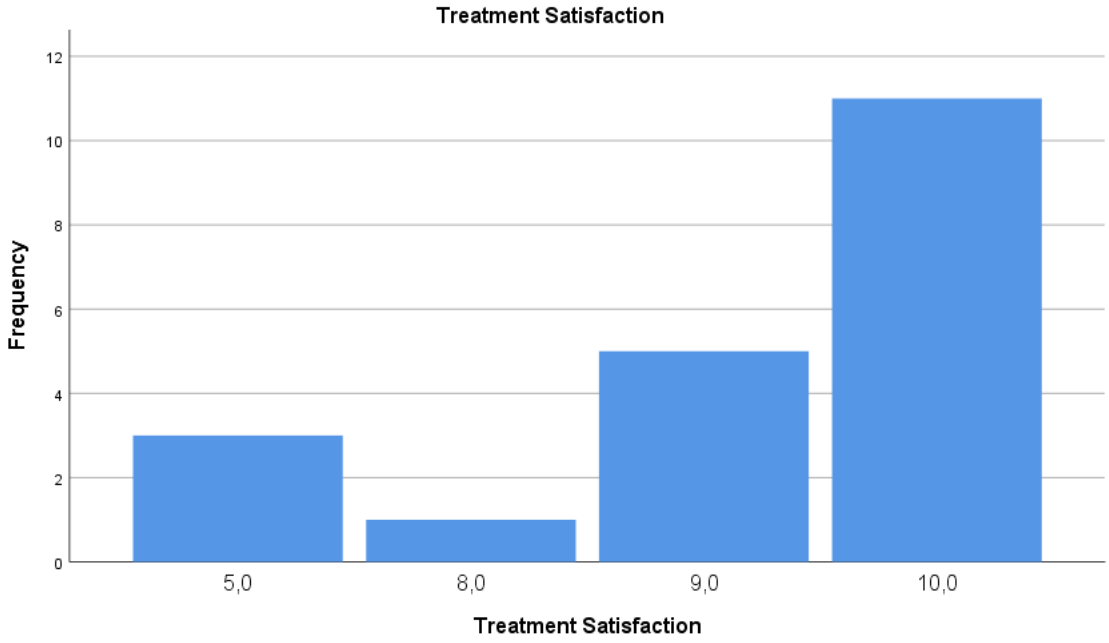

Figure 3 - Treatment satisfaction at last appointment: descriptive analysis

The 3 treatment groups (oral MTX, subcutaneous MTX and bDMARD monotherapy) reported similar levels of satisfaction with the treatment they were receiving (Table 10).

Table 10 – Satisfaction with oral MTX versus SC MTX versus bDMARD monotherapy

	Oral MTX	SC MTX	bDMARD monotherapy	*p-value*
Satisfaction NRS Median (IQR)	10 (1.5)	9.5 (5)	10 (1)	0.75

bDMARD – Biologic disease-modifying antirheumatic drugs; MTX – Methotrexate; NRS – Numerical rating scale; SC – Subcutaneous

- School problems

Twenty four out of the 26 patients attended school. Some patients and their parents reported school-related problems caused by JIA. 4 patients reported having difficulties in remaining seated for a long time, 3 patients reported numerous absences, 2 patients reported decreased performance at school and 3 patients reported problems at Physical Education classes.

- **Effectiveness of MTX**

The response to MTX was evaluated at 6 and 12 months after treatment start, separately for each treatment course. MTX was used earlier in disease course, but otherwise disease activity and function were not significantly different between those who started oral and those who started subcutaneous MTX (supplementary Table I). MTX monotherapy was numerically higher with subcutaneous route (76%) than with oral (62%), but the difference is not statistically significant (supplementary Table II).

- Response to MTX

Taking into account the Responders vs Non-responders definition – achieving minimal disease activity according to JADAS definition for oligoarticular ($\leq$2) and for polyarticular ($\leq$3.8) JIA, or showing an improvement of at least 50% in the number of active joints and did not start a biologic or receive systemic or intra-articular glucocorticoids – there is no statistically significant difference between each route of administration in

achieving minimal disease activity at 6 and 12 months after MTX treatment start (*p-value* = 0.495 and 0.199).

The results are presented in Tables 11 and 12.

Table 11 – Response to MTX at 6 months

	Total N=43	Subcutaneous N=16	Oral N=27
Responders N (%)	27 (62.8)	9 (56.2)	18 (66.7)
Non-responders N (%)	16 (37.2)	7 (43.8)	9 (33.3)
p-value	0.495		

Table 12 – Response to MTX at 12 months

	Total N=35	Subcutaneous N=13	Oral N=22
Responders N (%)	21 (60)	6 (46.2)	15 (68.2)
Non-responders N (%)	14 (40)	7 (53.8)	7 (31.8)
p-value	0.199		

- Response to MTX

Improvement of JADAS and of its components was assessed at 6 and 12 months for each route of administration of MTX. Results are summarized in Table 13.

There is a statistically significant difference in the variation of JADAS at 6 months of MTX treatment (*p-value* = 0.02), in the variation of the VAS for pain (*p-value* = 0.046) and in the variation of the inflammatory marker ESR (*p-value* = 0.015) between the routes of administration, being the reduction more pronounced with subcutaneous MTX.

At 12 months of methotrexate treatment, the reduction of pain was also significantly higher for subcutaneous administration (*p-value* = 0.047).

Table 13 – Improvement of JADAS at 6 and 12 months of methotrexate treatment

Variable	*6 months*				*12 months*			
	N	SC	Oral	*p-value**	N	SC	Oral	*p-value**
Δ JADAS	21	-8.97	-3.9	**0.02**	19	-8.7	-4.7	0.09
Δ Tender joints	42	-2	-1	0.69	34	-2	-2	0.6
Δ Swollen joints	41	-1.5	-1	0.968	32	-2.1	-1.4	0.24
Δ VAS pain	25	-38.1	-17.8	**0.046**	24	-38.4	-16.5	**0.047**
Δ ESR	39	-18	-7	**0.015**	29	-10	-5.5	0.46
Δ CPR	37	-0.3	0	0.769	30	-0.2	-0.2	0.25
Δ C-HAQ	6	0	-0.1	0.667	4	-0.2	-0.4	0.67

**T-student or Mann-Whitney test p-value* according to the normality tests.

C-HAQ – Childhood Health Assessment Questionnaire; CPR – C-reactive protein; ESR – Erythrocyte sedimentation rate; JADAS – Juvenile Arthritis Disease Activity Score; SC – subcutaneous; VAS – Visual Analogic Scale

- **Safety of MTX**

During the follow-up, some children have discontinued MTX treatment for different reasons and some adverse reactions have been reported.

2 patients have discontinued MTX treatment because of gastrointestinal intolerance, namely nausea. 3 patients had sustained transaminases elevation during MTX treatment: 2 of them have suspended treatment and 1 has adjusted MTX dosage with improvement. 2 patients have discontinued MTX because of disease remission and 1 patient for therapeutic refusal.

1 patient has switched the route of administration from oral to subcutaneous because of gastrointestinal intolerance.

Of those patients discontinuing treatment because of gastrointestinal intolerance, 1 was under subcutaneous MTX and the other was under oral MTX treatment. The 2 patients with transaminases elevation that led to discontinuation were under subcutaneous MTX treatment.

The 2 patients that have achieved remission were under oral MTX treatment.

Of the 20 patients under a csDMARD or bDMARD treatment at last appointment, 3 reported having troubles related to the medication: 1 was taking oral MTX and reported having sleep disturbances, 1 was taking subcutaneous MTX and reported having nausea and vomiting, swollen/bleeding gums, and mouth sores and 1 was taking subcutaneous MTX + adalimumab and reported having mood swings.

Besides, 6 of these 20 patients have reported difficulties in the administration of the medication on a regular basis: 1 patient taking subcutaneous MTX + adalimumab reported difficulty in the administration of adalimumab; 1 patient taking oral MTX + adalimumab, 1 patient taking subcutaneous MTX + adalimumab and 2 patients taking oral MTX alone reported difficulty in the administration of MTX and 1 patient taking Etanercept reported difficulties in the injection administration.

Discussion

The safety and efficacy of MTX in JIA were first reported more than 25 years ago. Both physical and psychosocial dimensions of quality of life have also been found to improve in children with JIA treated with MTX. Nevertheless, difficulties in the administration of MTX are experienced by children with JIA, particularly because of side effects and fear of subcutaneous administration, that may negatively affect their quality of life, beyond the impact of the disease itself.

Our study documents an excellent quality of life and satisfaction with treatment reported by children and adolescents with JIA and their parents, regardless of treatment used (none, csDMARD, bDMARD). Most children classified as having “no problems” in all EQ-5D-Y dimensions. Furthermore, more than three quarters of children classified their health higher than 90/100.

Additionally, in our patients with JIA, the route of administration of MTX seems to have no influence on the quality of life, being similarly good in both groups.

More than three quarters of children classified their satisfaction with treatment as 9 or 10/10.

Of note, JIA children and adolescents had their disease activity well controlled, which probably contributes to this result. At last appointment, the median JADAS was 1.3, value that corresponds to physician-assessed remission ($\leq$2). Furthermore, most children had no swollen or tender joints at last appointment.

The response to MTX, in terms of JADAS reduction at 6 months and reduction of pain, was better with subcutaneous MTX than with oral MTX treatment. However, the dosage of subcutaneous MTX was significantly higher, which can explain this difference.

Four patients, 3 on subcutaneous and 1 on oral MTX treatment, have discontinued MTX treatment because of adverse reactions. We did not find any differences between tolerability of oral and subcutaneous MTX, despite a higher dose used subcutaneously.

Subcutaneous route of administration may have allowed the use of higher doses, otherwise not tolerated orally, which can contribute to a better control.

There is limited information about effectiveness and safety of oral versus subcutaneous MTX for the treatment of JIA available in the literature (Klein et al., 2012). Some studies reported no differences in effectiveness between the two routes of MTX administration. However, other investigators have shown increased bioavailability at higher doses with the use of subcutaneous MTX, as well as increased efficacy after switching from oral to subcutaneous administration (Giancane et al., 2016). It has been shown that subcutaneous administration of MTX has a 10–12% increased absorption compared with oral administration (Ramanan & Whitworth, 2003), which could explain the potential better responses with this route of administration.

Several authors have reported a higher frequency of intolerance with subcutaneous administration of MTX, namely post-administration vomiting, while others have found no differences or fewer adverse reactions (Barral Mena et al., 2020; Mulligan et al., 2013).

An observational study (Klein et al., 2012) with patients from the German Methotrexate Registry concluded that parenteral MTX is not superior to oral MTX regarding efficacy and tolerability.

In our cohort, the safety of MTX was similar with subcutaneous and oral MTX, although the subcutaneous route allowed using higher doses and achieving greater reduction of JIA disease activity.

Although we have no information on the reason for choosing between the routes of administration, the similarity of baseline JIA disease activity and function in the two groups does not suggest this was a decisive factor in the choice between oral and subcutaneous MTX.

This study has several limitations, namely: 1) the small population size and consequently, the small sample for each of the treatment courses and routes of administration; 2) its retrospective design and some missing clinical information; 3) results are presented as observed (crude data) with no adjustments for potential confounders due to sample size; 4) the reasons for switching the route of administration in a single patient (resulting in several treatment courses), as well as the reasons to start with one route of administration versus the other were not always recorded and inferable from the database.

In conclusion, the perspective of the patients and their parents regarding JIA treatments is very important, must be valued and incorporated in the clinical decision-making process.

Despite potential difficulties with MTX use, the quality of life and the overall satisfaction with treatment are very good and not related to the route of administration.

The confirmation of our results in a different cohort will be important to inform clinicians about the optimal use of MTX in order to achieve the best outcome for each patient.

Agradecimentos

Gostaria de utilizar este espaço para agradecer a algumas pessoas que me acompanharam neste percurso na Faculdade de Medicina de Lisboa, que culmina com a defesa deste Trabalho Final de Mestrado.

Em primeiro lugar, agradecer à minha orientadora e co-orientadora, Professora Dra. Maria José Santos e Dra. Sandra Nunes Sousa, por me fazerem sair da minha zona de conforto e pela disponibilidade, acompanhamento e aprendizagem. Agradeço por aceitarem este desafio e por me desafiarem.

À minha família, aos meus pais e avós, por serem o meu porto de abrigo. Pelo apoio incondicional, pelo carinho e pelo exemplo.

Ao Kiko, irmão e amigo, por ser o meu corretor linguístico oficial. À Cati e à Nô, por serem as minhas fãs número um.

À Mónica, Raquel e Tânia, por me acompanharem nesta viagem. Pelas crises conjuntas, por todas as dúvidas ultrapassadas, pelo apoio e pela amizade. Pelos 6 anos desta aventura, pelo caminho bonito que começámos juntas.

À Mariana e ao Tomás por me valorizarem, por me estimarem e por me incentivarem a ser melhor pessoa e melhor médica. Por serem bússolas quando me sinto perdida.

À Leonie, Maria e Mariana, pela amizade, pelos desabafos, aventuras e sorrisos, que enriqueceram esta caminhada.

Aos meus companheiros e colegas médico-musicais, por me completarem, por me fazerem sonhar e pelas memórias que guardo com tanto carinho,

Obrigada.

Madalena

References

Barral Mena, E., García Cárdaba, L. M., Canet Tarrés, A., Enríquez Merayo, E., Cruz Utrilla, A., & de Inocencio Arocena, J. (2020). Methotrexate in juvenile idiopathic arthritis. Adverse effects and associated factors. *Anales de Pediatría (English Edition)*, *92*(3), 124–131. https://doi.org/10.1016/j.anpede.2019.05.011

Crayne, C. B., & Beukelman, T. (2018). Juvenile Idiopathic Arthritis: Oligoarthritis and Polyarthritis. *Pediatric Clinics of North America*, *65*(4), 657–674. https://doi.org/10.1016/j.pcl.2018.03.005

Ferrara, G., Mastrangelo, G., Barone, P., la Torre, F., Martino, S., Pappagallo, G., Ravelli, A., Taddio, A., Zulian, F., & Cimaz, R. (2018). Methotrexate in juvenile idiopathic arthritis: Advice and recommendations from the MARAJIA expert consensus meeting. *Pediatric Rheumatology*, *16*(1). https://doi.org/10.1186/s12969-018-0255-8

Giancane, G., Consolaro, A., Lanni, S., Davì, S., Schiappapietra, B., & Ravelli, A. (2016). Juvenile Idiopathic Arthritis: Diagnosis and Treatment. *Rheumatology and Therapy*, *3*(2), 187–207. https://doi.org/10.1007/s40744-016-0040-4

Kearsley-Fleet, L., Vicente González, L., Steinke, D., Davies, R., de Cock, D., Baildam, E., Beresford, M. W., Foster, H. E., Southwood, T. R., Thomson, W., & Hyrich, K. L. (2019). Methotrexate persistence and adverse drug reactions in patients with juvenile idiopathic arthritis. *Rheumatology (United Kingdom)*, *58*(8), 1453–1458. https://doi.org/10.1093/rheumatology/kez048

Klein, A., Kaul, I., Foeldvari, I., Ganser, G., Urban, A., & Horneff, G. (2012). Efficacy and safety of oral and parenteral methotrexate therapy in children with juvenile idiopathic arthritis: An observational study with patients from the German Methotrexate Registry. *Arthritis Care & Research*, *64*(9), 1349–1356. https://doi.org/10.1002/acr.21697

Mulligan, K., Kassoumeri, L., Etheridge, A., Moncrieffe, H., Wedderburn, L. R., & Newman, S. (2013). Mothers' reports of the difficulties that their children

experience in taking methotrexate for Juvenile Idiopathic Arthritis and how these impact on quality of life. *Pediatric Rheumatology*, *11*(1). https://doi.org/10.1186/1546-0096-11-23

Ramanan, A. v, & Whitworth, P. (2003). Use of methotrexate in juvenile idiopathic arthritis. *Arch Dis Child*, *88*, 197–200. www.archdischild.com

Santos, M. J., Conde, M., Mourão, A. F., Ramos, F. O., Cabral, M., Brito, I., Ramos, M. P., Marques, R. C., Gomes, S. M., Guedes, M., Gonçalves, M. J., Estanqueiro, P., Zilhão, C., Rodrigues, M., Henriques, C., Salgado, M., Canhão, H., Fonseca, J. E., & Gomes, J. M. (2016). 2016 update of the Portuguese recommendations for the use of biological therapies in children and adolescents with Juvenile Idiopathic Arthritis. *Acta Reumatologica Portuguesa*, *41*(3), 194–212. https://www.researchgate.net/publication/310488446

Annexes

Annex I

I – Demographic and clinical characteristics for each route of methotrexate administration at baseline

Variable	SC *	Oral *	*p-value*
Age (N=46)	7.6	5.7	0.357
Years since first appointment (N=40)	5.7	0.3	**0.011**
Weight (N=43) *Kg*	24	18	0.364
Height (N=35) *cm*	120.5	112	0.781
Tender joints (N=43)	2	2	0.868
Swollen joints (N=42)	2	2	0.266
ESR mm/h (N=42)	23	22	0.837
CRP mg/dL (N=40)	0.5	0.5	1
JADAS27 (N=29)	10.7	7.1	0.296
C-HAQ (N=13)	0.25	0	1

*median value

II- Concomitant medication for each route of administration

	Subcutaneous	Oral	Total
Monotherapy	13	18	31
GC	1	2	3
bDMARD	3	7	10
SA + GC	0	1	1
bDMARD + GC	0	1	1
Total	17	29	46
chi-square p-value	0.468		

bDMARD – Biologic disease-modifying antirheumatic drugs; GC – Glucocorticoid; SA – Sulfasalazine;

Annex II

HOSPITAL Garcia de Orta E.P.E. A referência a Sul

PARECER E AUTORIZAÇÃO PARA REALIZAÇÃO DE ESTUDO

Hospital Garcia de Orta EPE
Centro de Investigação Hospital Garcia de Orta

Título: Projecto intitulado " Impacto da terapêutica com metotrexato oral versus subcutâneo na qualidade de vida das crianças com artrite idiopática juvenil".
Investigador Principal: Dra Sandra Sousa

A **Comissão de Ética** para a Saúde do Hospital Garcia de Orta informa que o trabalho em epígrafe obteve parecer positivo por unanimidade ☒ maioria ☐ em reunião do dia 20/09/2021.

Estiveram presentes:

☒ Nome: Dra Natália Dias (Presidente)
☒ Nome: Dra Ana Soares
☒ Nome: Dra Benedita Nunes
☐ Nome: Dra Cátia Gradil
☒ Nome: Dra Isabel Pereirinha
☐ Nome: Dr. José Luis Metello
☐ Nome: Dra Maria Gomes Ferreira
☒ Nome: Dr. Miguel Rodrigues
☒ Nome: Enfª Teresa Chambel

A CES solicita ao Investigador Principal que quando da conclusão deste estudo, lhe seja enviada uma síntese dos resultados e conclusões do mesmo.

Dra. Natália Dias
Presidente da Comissão de Ética

O Estudo em epígrafe foi aprovado pelo **Conselho de Administração** em reunião do dia 23/09/2021.

Dra. Paula Breia
Presidente do Centro Garcia de Orta

Almada, 30/09/2021

Annex III

HOSPITAL Garcia de Orta E.P.E.

ASSENTIMENTO DE MENOR 12 a 15 ANOS

Queremos perguntar-te se queres participar na nossa investigação para avaliar a qualidade de vida das crianças e adolescentes com Artrite Idiopática Juvenil (AIJ). Antes de decidires se queres participar, fala com a tua família, e faz as perguntas que quiseres ao médico ou enfermeiro. Se decidires que queres participar, vamos fazer-te algumas perguntas e irás preencher dois questionários sobre a forma como te sentes.

A decisão para participar é completamente tua. Se não quiseres basta dizer-nos. Independentemente do que decidires, ninguém se vai aborrecer e também não irá mudar a forma como és tratado(a). Se decidires participar, irás assinar um documento para dizer que compreendes o que irá acontecer e que participas de livre vontade. Os teus pais também terão que assinar um documento para dizer que estão de acordo com a tua participação. A tua participação na investigação irá ajudar-nos a perceber melhor o impacto do tratamento com metotrexato na tua doença e na tua vida.

Se quiseres participar neste estudo, depois de termos falado, escreve o teu nome em baixo. Também iremos escrever o nosso nome. Isto mostra que falámos sobre o estudo e que aceitas participar.

NOME DO PARTICIPANTE: _____

_____ _____

Data Assinatura do participante

Discuti este estudo de investigação com o participante e com os pais/ou o seu representante legal, utilizando uma linguagem compreensível e apropriada. Informei adequadamente o participante sobre a natureza deste estudo e sobre os seus possíveis benefícios e riscos, considerando que o participante compreendeu a minha explicação.

Nome do médico do estudo _____

_____ _____

Data Assinatura do Médico do estudo

Annex IV

HOSPITAL Garcia de Orta E.P.E.

CONSENTIMENTO INFORMADO PARA PARTICIPANTE 16-17 ANOS

Impacto da terapêutica com metotrexato oral versus subcutâneo na qualidade de vida das crianças com Artrite Idiopática Juvenil

Estamos a convidar-te para participar neste estudo de investigação cujo objetivo principal é avaliar a qualidade de vida das crianças e jovens com Artrite Idiopática Juvenil (AIJ) sob terapêutica com metotrexato. Iremos incluir cerca de 30 participantes seguidos em consulta de Reumatologia Pediátrica no Hospital Garcia de Orta.

Este consentimento só é válido juntamente com o consentimento parental

A participação no estudo é voluntária. Tens toda a liberdade para recusar participar ou de retirar o consentimento sem ter que justificar o motivo, suspendendo a participação em qualquer momento. A recusa em participar não envolverá qualquer penalização ou colocará em risco o direito a receber tratamento ou assistência médica, presentemente ou no futuro, nesta instituição.
Este estudo obteve a aprovação da Comissão de Ética do Hospital Garcia de Orta e será conduzido sob a supervisão da Dr.ª Sandra Sousa.

Descrição e Métodos do Estudo: A tua participação neste estudo incluirá a obtenção de um consentimento informado e a resposta a dois questionários. Esta informação será posteriormente analisada juntamente com dados obtidos na prática clínica habitual.
A participação no estudo não irá alterar a avaliação clínica habitual ou a periodicidade da mesma definida pelo médico assistente, nem implica realização de quaisquer análises ou outros exames complementares.

Riscos e benefícios: Não são expectáveis quaisquer riscos decorrentes da participação no estudo e não terás quaisquer benefícios, mas ao participar neste estudo estás a contribuir para conhecermos melhor o impacto da terapêutica com metotrexato na qualidade de vida de crianças e jovens com AIJ

Confidencialidade e privacidade: Ao participar, estás ciente dos objetivos desta investigação e aceita que a informação clínica seja recolhida através da consulta do processo clínico. O nome e número do processo clínico serão mantidos em local seguro, só a equipa do estudo terá acesso a eles e apenas serão utilizados para os fins descritos neste documento. Os resultados deste estudo serão apresentados sob a forma relatório e poderão dar lugar à publicação de artigos científicos, dissertação e/ou trabalho académico, mas a tua identificação nunca será divulgada. Os dados recolhidos especificamente para este estudo serão destruídos um ano após conclusão do mesmo. Se considerares que os teus dados pessoais foram indevidamente utilizados tens o direito a apresentar uma reclamação junto do encarregado de proteção de dados do Hospital Garcia de Orta (DPO@hgo.min-saude.pt) ou junto da Comissão Nacional de Proteção de Dados (geral@cnpd.pt).

Se tiver qualquer dúvida, em qualquer momento sobre este estudo, poderá contactar:

Dra. Sandra Sousa, Serviço de Reumatologia, Hospital Garcia de Orta;
Telefone: 212723775;
Email: sandra.isabel.sousa@hgo.min-saude.pt

DECLARAÇÃO DE CONSENTIMENTO INFORMADO PARA PARTICIPANTE 16-17 ANOS

Impacto da terapêutica com metotrexato oral versus subcutâneo na qualidade de vida das crianças com Artrite Idiopática Juvenil

Declaro que li este formulário, que todas as minhas questões foram adequadamente respondidas e que aceito participar nesta investigação. Confirmo fazê-lo livre de quaisquer pressões ou receios.

Recebi uma cópia desta declaração de consentimento informado, devidamente assinada e datada.

Nome do participante _____

_____ _____

Data Assinatura do Participante

Discuti este estudo de investigação com o participante e com os pais e/ou representante legal, utilizando uma linguagem compreensível e apropriada. Informei adequadamente sobre a natureza deste estudo e sobre os seus possíveis benefícios e riscos, considerando que os compreenderam a minha explicação.

Nome do médico do estudo _____

_____ _____

Data Assinatura do Médico do estudo

Annex V

HOSPITAL Garcia de Orta E.P.E.

CONSENTIMENTO INFORMADO PARENTAL

Impacto da terapêutica com metotrexato oral versus subcutâneo na qualidade de vida das crianças com Artrite Idiopática Juvenil

Estamos a convidar o seu filho para participar neste estudo de investigação cujo objetivo principal é avaliar a qualidade de vida das crianças e jovens com Artrite Idiopática Juvenil (AIJ) sob terapêutica com metotrexato. Iremos incluir cerca de 30 participantes seguidos em consulta de Reumatologia Pediátrica no Hospital Garcia de Orta.
A participação no estudo é voluntária. Tem toda a liberdade para recusar a participação do seu filho ou de retirar o seu consentimento sem ter que justificar o motivo, suspendendo a participação em qualquer momento. A recusa em participar não envolverá qualquer penalização ou colocará em risco o direito do seu filho a receber tratamento ou assistência médica, presentemente ou no futuro, nesta instituição.
Este estudo obteve a aprovação da Comissão de Ética do Hospital Garcia de Orta e será conduzido sob a supervisão da Dr.ª Sandra Sousa.

Descrição e Métodos do Estudo: A participação do seu filho neste estudo incluirá a obtenção de um consentimento informado e a resposta a dois questionários. Esta informação será posteriormente analisada juntamente com dados obtidos na prática clínica habitual.
A participação no estudo não irá alterar a avaliação clínica habitual ou a periodicidade da mesma definida pelo médico assistente, nem implica realização de quaisquer análises ou outros exames complementares.

Riscos e benefícios: Não são expectáveis quaisquer riscos decorrentes da participação no estudo e não terá benefícios, mas ao participar neste estudo está a contribuir para conhecermos melhor o impacto das várias formas de administração da terapêutica com metotrexato na qualidade de vida de crianças e jovens com AIJ.

Confidencialidade e privacidade: Ao participar, está ciente dos objetivos desta investigação e aceita que a informação clínica seja recolhida através da consulta do processo clínico do seu filho. O nome e número do processo clínico serão mantidos em local seguro, só a equipa do estudo terá acesso a eles e apenas serão utilizados para os fins descritos neste documento. Os resultados deste estudo serão apresentados sob a forma de relatório e poderão dar lugar à publicação de artigos científicos, dissertação e/ou trabalho académico, mas a identificação do seu filho nunca será divulgada. Os dados recolhidos especificamente para este estudo serão destruídos um ano após conclusão do mesmo. Se considerar que os dados pessoais do seu filho foram indevidamente utilizados tem direito a apresentar uma reclamação junto do encarregado de proteção de dados do Hospital Garcia de Orta (DPO@hgo.min-saude.pt) ou junto da Comissão Nacional de Proteção de Dados (geral@cnpd.pt).

Se tiver qualquer dúvida, em qualquer momento sobre este estudo, poderá contactar:
Dra. Sandra Sousa, Serviço de Reumatologia, Hospital Garcia de Orta;
Telefone: 212723775;
Email: sandra.isabel.sousa@hgo.min-saude.pt

DECLARAÇÃO DE CONSENTIMENTO INFORMADO PARENTAL

Para os pais e/ou representantes legais

Impacto da terapêutica com metotrexato oral versus subcutâneo na qualidade de vida das crianças com Artrite Idiopática Juvenil

Declaro que li este formulário, que todas as minhas questões foram adequadamente respondidas e que aceito que o meu filho participe nesta investigação. Confirmo fazê-lo livre de quaisquer pressões ou receios.

Recebi uma cópia desta declaração de consentimento informado, devidamente assinada e datada.

Nome do pai _____

_____ _____

Data Assinatura do pai /Representante Legal

Nome da mãe _____

_____ _____

Data Assinatura da mãe /Representante Legal

Discuti este estudo de investigação com os pais e/ou representante legal do participante, utilizando uma linguagem compreensível e apropriada. Informei adequadamente sobre a natureza deste estudo e sobre os seus possíveis benefícios e riscos, considerando que os progenitores/representante legal compreenderam a minha explicação.

Nome do médico do estudo _____

_____ _____

Data Assinatura do Médico do estudo