ORIGINAL ARTICLE

Adherence to Disease Modifying Anti Rheumatic Drugs in Tunisian patients with Juvenile Idiopathic Arthritis: An Observational study

Observance des traitements de fond chez les patients Tunisiens atteints d'Arthrite Juvénile Idiopathique

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Abstract

Introduction: Non-adherence or poor therapeutic adherence appears to be particularly prevalent in chronic inflammatory rheumatism, notably in Juvenile Idiopathic Arthritis (JIA). It reduces therapeutic efficacy, accelerates disease progression, and poses a significant public health and economic challenge.

Aim: To evaluate adherence to disease-modifying treatments in Tunisian patients with JIA and to identify factors influencing therapeutic adherence.

Methods: This cross-sectional study included patients with JIA (defined by ILAR criteria) who had been undergoing treatment with conventional synthetic (csDMARDs) and/or biologic (bDMARDs) disease-modifying anti-rheumatic drugs for at least three months. Socio-demographic, clinical, biological, radiological, and therapeutic data were collected. Therapeutic adherence was assessed using two methods: self-reported adherence by patients and their parents, and adherence measured via the Parent Adherence Report Questionnaire (PARQ) and the Child Adherence Report Questionnaire (CARQ).

Results: A total of 30 patients (16 girls, 14 boys) with a mean age of 24.8 ± 11 years [8-47] were included. csDMARDs were prescribed for 76.7% of patients while 26.7% received bDMARDs. Self-reported adherence was 80% among parents and 76.7% among patients. Mean adherence scores were 74.58 ± 36 [0-100] on the PARQ and 74 ± 34 [0-100] on the CARQ. Univariate analysis revealed that adherence measured by the PARQ was positively correlated with erythrocyte sedimentation rate (ESR) (p=0.001; r=0.643) and C-reactive protein (CRP) (p=0.008; r=0.561) and negatively correlated with maternal age (p=0.005; r=-0.572), difficulty in medication administration reported by the parent (p<0.0001; r=-0.698), and negative reactions to medication reported by both the patient (p=0.012; r=-0.506) and the parent (p=0.001; r=-0.651). Adherence measured by the CARQ was significantly associated with indigent health insurance status (p=0.019). In multivariate analysis, predictors of non-adherence on the PARQ included advanced maternal age (p=0.004), low ESR (p=0.029), and negative reactions to medications (p<0.0001). On the CARQ, difficulty in adhering to the treatment regimen (p=0.042) was the only significant predictor.

Conclusion: This study demonstrates good therapeutic adherence among Tunisian patients with JIA. Predictors of non-adherence included advanced maternal age, low disease activity, negative reactions to medications, and difficulties in following treatment regimens. Educational strategies targeting these factors may improve adherence and enhance patient outcomes.

Key words: disease modifying anti rheumatic drugs, compliance, adherence, juvenile idiopathic arthritis

Résumé

Introduction: La non- ou la mauvaise observance thérapeutique semble particulièrement fréquente au cours des rhumatismes inflammatoires chroniques et notamment au cours de l'Arthrite Juvénile Idiopathique (AJI). Elle est à l'origine d'une réduction du potentiel thérapeutique, d'une aggravation et d'une progression de la maladie et représente de ce fait un réel enjeu sanitaire et économique.

Objectif: Évaluer l'observance des traitements de fond chez les patients tunisiens atteints d'AJI ainsi que les potentiels facteurs pouvant influencer cette observance.

Méthodes: Il s'agit d'une étude transversale incluant des patients atteints d'AJI (critères ILAR), ayant un traitement en cours par csDMARDs et/ou bDMARDs débuté depuis au moins 3 mois. Les données socio démographiques, cliniques, biologiques, radiologiques et thérapeutiques ont été recueillies.

L'observance thérapeutique a été évaluée en utilisant deux méthodes : l'observance déclarée par le patient et le parent et l'observance mesurée grâce à deux auto-questionnaires : le PARQ « Parent Adherence Report Questionnaire » et le CARQ « Child Adherence Report Questionnaire ».

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Résultats: Trente patients, 16 filles et 14 garçons, âgés en moyenne 24,8 ± 11 ans [8-47] ont été inclus. Un csDMARD a été prescrit chez 76,7% des patients et un bDMARD chez 26,7%. Quatre-vingts pourcents des parents et 76,7 % des patients ont déclaré prendre leur traitement comme prescrit. L'observance thérapeutique selon le PARQ et le CARQ avait une moyenne de 74,58 ± 36 [0-100] et de 74 ± 34 [0-100] respectivement. Dans l'analyse univariée, l'observance thérapeutique selon le PARQ était positivement corrélée à la VS (p=0,001; r=0,643) et à la CRP (p=0,008; r=0,561) et négativement corrélée à l'âge de la mère (p=0,005; r=-0,572), à la difficulté de prise des médicaments selon le parent (p<0,0001; r=-0,698) et aux réactions négatives aux médicaments selon le patient (p=0,012; r=-0,506) et le parent (p=0,001; r=-0,651). L'observance thérapeutique selon le CARQ était significativement liée à la couverture sociale de type « carnet indigent » (p=0,019). Dans l'analyse multivariée, les facteurs prédictifs de non-observance selon le PARQ étaient l'âge élevé de la mère (p=0,004), le faible taux de la VS (p=0,029) et les réactions négatives aux médicaments (p<0,0001). Pour le CARQ, le seul facteur pourvoyeur de non-observance était la difficulté à suivre les traitements (p=0,042) selon le parent.
Conclusion: Notre étude a montré une bonne observance thérapeutique chez les patients tunisiens présentant une AJI. L'âge élevé de la mère, la faible activité de la maladie, les réactions négatives aux médicaments et la difficulté à suivre les traitements étaient prédictifs d'une non-observance médicamenteuse. Des stratégies éducatives adéquates permettraient d'améliorer l'observance et ainsi le pronostic des patients atteints d'AJI.

Mots clés: médicaments antirhumatismaux modificateurs de la maladie, conformité, adhésion, arthrite juvénile idiopathique

Introduction

Disease-modifying therapies for chronic inflammatory rheumatism (CIR) have significantly evolved over recent decades, resulting in improved quality of life for many patients. However, non-adherence or suboptimal adherence to therapy remains a pervasive issue in these chronic conditions, representing a substantial health and economic challenge. Non-adherence undermines therapeutic efficacy, accelerates disease progression, and contributes to a significant socio-economic burden through increased healthcare utilization and reduced productivity [1-3].

Despite the considerable impact of non-adherence in CIR, especially in Juvenile Idiopathic Arthritis (JIA) [4-6], limited studies have specifically addressed this issue. To date, no studies in Tunisia have assessed therapeutic adherence in JIA.

The primary aim of our study was to assess adherence to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologic disease-modifying anti-rheumatic drugs (bDMARDs) in Tunisian patients with JIA using self-administered questionnaires. Additionally, we sought to identify factors influencing adherence.

Methods

Study population

This cross-sectional study included patients with JIA who fulfilled the 2001 criteria established by the International League of Associations for Rheumatology (ILAR). Eligible participants were those undergoing treatment with csDMARDs and/or bDMARDs for a minimum duration of three months and were being followed at the rheumatology department.

Patients were excluded if they had permanently discontinued their disease-modifying treatment or had hearing, speech, or cognitive impairments that could hinder accurate completion of the questionnaires.

Data collection was carried out through patient and parent interviews, as well as a review of medical records. This approach facilitated the gathering of socio-demographic information, disease duration, and clinical-biological parameters of disease activity, including: visual analog scale (VAS) for pain, global patient assessment (GPA), duration of morning stiffness (MS), number of night awakenings (NA), tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), juvenile arthritis disease activity score (JADAS)-10 [7], Childhood Health Assessment Questionnaire (C-HAQ) [7] to evaluate functional impact. Additional data included the immunological profile, presence of extra-articular manifestations, radiographic findings, and details of the current disease-modifying therapy regimen.

Measuring therapeutic compliance

Therapeutic compliance was assessed using two complementary methods: self-reported adherence by both the patient and their parent, and compliance evaluation through two self-administered questionnaires distributed separately to the patient and one of their parents.

Self-reported adherence was initially evaluated with a direct question : "*Do you or your child take the prescribed treatment regularly as recommended by the rheumatologist ?*" If the response was negative, the reasons for non-adherence were documented.

Parents completed the Parent Adherence Report Questionnaire (PARQ), which measures the child's therapeutic adherence as perceived by the parent. Patients with JIA filled out the Child Adherence Report Questionnaire (CARQ), a self-reported tool designed to assess their own adherence. Both the PARQ and CARQ were administered in their validated French versions [8].

Responses to the PARQ and CARQ are scored on a scale ranging from 0 (no adherence) to 100 (complete adherence), with higher scores indicating better compliance. The PARQ evaluates adherence across three specific themes : medication, exercise, and orthosis use. For each theme, parents assess four dimensions : The frequency with which their child adheres to the treatment, the perceived difficulty in following the treatment, the frequency of negative reactions from the child (e.g., crying, complaining, or refusal to cooperate), the parent's opinion on the treatment's usefulness.Parents were also asked to specify their preferred treatment. Each question in the PARQ is scored individually, allowing for detailed analysis of specific adherence behaviors.

The CARQ is a child-adapted version of the PARQ. While maintaining a similar structure and scoring system, its language and syntax have been simplified to

accommodate children's comprehension levels [8].
Both questionnaires were completed independently by patients and their parents. For participants who were illiterate or had only primary-level education, assistance was provided to ensure accurate completion of the forms.

Statistical study
Data were entered using Excel 2019 and analysed with SPSS version 25.0.
Descriptive analysis
Frequencies and relative frequencies (percentages) were calculated for qualitative variables, while means, medians, quartiles (P25 and P75), standard deviations, and ranges were used to summarize quantitative variables.
Analytical analyses
Associations between qualitative variables were assessed using the chi-square test. Two-way associations between quantitative variables were examined using Spearman's rank correlation, with the p-value indicating statistical significance and Spearman's rho (r) representing the strength of the relationship.
A multivariate analysis using multiple linear regression was performed to identify predictors of therapeutic non-adherence. Variables with a p-value < 0.2 in the univariate analysis were included in the regression model. The Durbin-Watson test was used to validate model residuals. Predictors were evaluated using beta coefficients (β) and their corresponding 95% confidence intervals (CI).
Reliability and Agreement Measures
The Kappa measure of agreement (κ) was used to assess reliability between the two observers (parent and child). Agreement was considered significant when the p-value was ≤ 0.05. Kappa values were interpreted as follows: <0 (disagreement), 0-0.20 (very weak agreement), 0.21-0.40 (weak agreement), 0.41-0.60 (moderate agreement), 0.61-0.80 (strong agreement), 0.81-0.99 (excellent agreement), and 1.00 (perfect agreement).
Kendall's tau-b correlation coefficient (τb) was employed to measure the strength and direction of the association between two variables, with values ranging from -1 (perfect negative correlation) to 1 (perfect positive correlation).

Results

Socio-demographic characteristics of the study population

The study included 30 patients with Juvenile Idiopathic Arthritis (JIA), with a sex ratio of 0.87 (14 boys to 16 girls). The mean age of the patients at the time of the study was 24.8 ± 11 years [8-47]. The mean age of the fathers was 59.6 ± 13 years [37-86] and the mean age of the mothers was 54.1 ± 10 years [34-75]. Twenty-five patients (83.3%) had health insurance, with the majority (56.7%) being covered by public health insurance. Most patients (76.7%) resided in urban areas, while 7 (23.3%) lived in rural areas. Of the 10 patients under 18 years of age, all were attending school (5 in primary school and 5 in secondary school). Among the 20 patients aged over 18, 14 were employed, 4 were in secondary school, and 2 were university students. Regarding parental status, 90% of the parents were married, while three patients had at least one deceased parent. Six fathers (22.2%) and seven mothers (25%) held a university degree. None of the fathers were illiterate, whereas 21.4% of the mothers were. All patients had siblings, with an average of three siblings per patient.

Characteristics of JIA

The clinical, biological and radiographic characteristics of patients with JIA patients are summarized in Table 1.

Table 1. Clinical, biological and radiographic characteristics of patients with JIA (n=30)

Variables	Values
Type of JIA, n (%)	
Systemic form	2 (7,7)
RF positive polyarticular form	4 (11,5)
RF negative polyarticular form	10 (34,6)
Oligoarticular form	10 (34,6)
Enthesitis related arthritis (ERA)	4 (11,5)
Psoriatic arthritis	0
Age of onset of JIA (years± SD)	7.4± 4
Duration of JIA progression (months ± SD)	209.2± 125
Activity parameters	
Average pain VAS (mm ± SD)	32.5± 27
Average GPA (mm± DS)	25.6± 26
Average number of NA (± SD)	0.17± 0
Average MS (minutes ± SD)	5.1± 9
Average TJC (± SD)	0.9± 1
Average SJC (± SD)	0.1± 1
Average ESR (mm± SD)	26.59± 28
Average CRP (mg/l) ± SD	12.85± 23
JADAS10-ESR medium± SD	7.65± 11
Functional impact	
Average C-HAQ± SD	0.24± 1
Extra-articular manifestations, n (%)	5 (16.7)
Presence of comorbidities, n (%)	0 (0)
Immunological profile	
RF positive, n (%)	6 (24)
ANA positive, n (%)	3 (12)
ACPA positive, n (%)	1 (4)
Radiographic data	
Erosive forms, n (%)	13 (44)
Coxitis, n (%)	11 (36.7)

SD: standard deviation, **n**: number of patients, **RF**: rheumatoid factor, **ACPA**: anti-citrullinated peptide antibodies, **ANA**: antinuclear antibodies, **VAS**: visual analog scale, **PGE**: patient global assessment, **NA**: number of night awakenings, **MR**: Duration of morning stiffness, **TJC**: tender joint count, **SJC**: swollen joint count, **ESR**: erythrocytes sedimentation rate, **CRP**: C Reactive Protein, **C-HAQ**: Childhood Health assessment Questionnaire, **JADAS 10**: Juvenile Arthritis Disease Activity Score

Regarding therapeutic characteristics, a csDMARD was prescribed to 76.7% of patients, with a mean treatment duration of 92.5 months [1-372]. The most commonly prescribed csDMARD was oral methotrexate (MTX), used in 65.2% of cases, followed by injectable MTX (13%), sulfasalazine (8.7%), and leflunomide (13%). csDMARDs were combined with a biologic bDMARD in 8 patients (33.3%) for an average duration of 40 months [7-85].

A bDMARD was prescribed to 26.7% of patients, with a mean treatment duration of 44.5 months [7-85]. The most frequently used bDMARD was etanercept (50%), followed by adalimumab (25%), infliximab (12.5%), and tocilizumab (12.5%). bDMARDs were prescribed as monotherapy in 12.5% of cases.

The route of administration for bDMARDs was subcutaneous in 6 cases (75%) and intravenous in 2 cases (25%). Subcutaneous injections were administered by one of the parents in 66.7% of cases. Long-term treatments associated with disease-modifying therapies included non-steroidal anti-inflammatory drugs (NSAIDs) in 7 patients (23.3%), with an average daily intake of 1.14 ± 0 tablets [1-2], and oral corticosteroids in 8 cases (26.7%), with an average daily intake of 1.38 ± 1 tablets [1-2].

Assessment of therapeutic compliance

A significant and strong positive correlation was found between the PARQ score and the parent's response to the direct adherence question (p = 0.002, r = 0.607). Similarly, the correlation between the CARQ score and the child's response to the direct question was also significant and strongly positive (p = 0.003, r = 0.525).

When asked, "*Do you (or does your child) take the prescribed treatment regularly as recommended by the rheumatologist?*", 80% of parents and 76.7% of children responded affirmatively. The reasons given by parents for non-adherence included fear of potential side effects (n = 3), forgetfulness (n = 1), and delays in treatment payment by the health insurance fund (n = 1). Among children, the most frequently cited reasons were fear of side effects (n = 5), forgetfulness (n = 1), and perceived ineffectiveness of the treatment (n = 1).

The PARQ and CARQ scores were generally high, with mean scores of 74.58 ± 36 [0-100] and 74 ± 34 [0-100], respectively, and median scores of 100 [52.5-100] and 100 [47.5-100], respectively.

Regarding treatment preferences, NSAIDs were the most favored by both parents and children (26.7%), followed by MTX (20%), corticosteroids (13.3%), and etanercept (10%). When asked, "*Why this treatment?*", 63.3% of parents and 20% of patients cited "*effectiveness against the disease*", 10% of patients mentioned "*ease of administration*", and 3.3% of both parents and children reported that the treatment "*had no side effects*".

The characteristics of the PARQ and CARQ are summarized in Table 2.

Study of parameters influencing therapeutic compliance

Univariate analysis

In the univariate analysis, therapeutic adherence assessed by the PARQ was positively correlated with (p=0.001; r=0.643) and CRP (p=0.008; r=0.561) levels. Conversely, it was negatively correlated with maternal age (p=0.005; r=-0.572), the parent's reported difficulty in administering medication (p<0.0001; r=-0.698), and negative reactions to medication reported by both the patient (p=0.012; r=-0.506) and the parent (p=0.001; r=-0.651).

Adherence measured by the PARQ was also significantly associated with the type of health insurance (p=0.014) and the route of bDMARD administration (p=0.022), with lower adherence observed among patients covered by "indigent" or "reduced-rate" insurance schemes, as well as those receiving intravenous bDMARDs.

Regarding adherence assessed by the CARQ, it was negatively correlated with patient age (p=0.036; r=-0.385), maternal age (p=0.029; r=-0.421), and disease duration (p=0.035; r=-0.386). It was also influenced by the difficulty in following treatment as reported by both the parent (p=0.001; r=-0.645) and the patient (p=0.002; r=-0.552), as well as by negative reactions to medication reported by the parent (p=0.011; r=-0.508). Finally, adherence according to the CARQ was significantly associated with the "indigent " health insurance scheme (p=0.019).

Table 2. Characteristics of PARQ and CARQ

	PARQ	CARQ
Responsibility for treatment administration		
• Medication, n (%)		
◦ Mother	14 (46.7)	10 (33.3)
◦ Father	0	1 (3.3)
◦ Child	16 (53.3)	19 (63.3)
• Exercises, n (%)		
◦ Mother	1 (3.3)	3 (10)
◦ Father	0	1 (3.3)
◦ Child	4 (13.3)	1 (3.3)
◦ Other: Siblings	1 (3.3)	1 (3.3)
Difficulty in following treatment		
• Medication, mean ± SD [Min-Max]	25.2 ± 35 [0-100]	26.3 ± 33 [0-100]
• Exercises, mean ± SD [Min-Max]	31.4 ± 39 [0-100]	37.1 ± 27 [0-70]
Adherence to treatment		
• Medication, mean ± SD [Min-Max]	74.5 ± 36 [0-100]	74 ± 34 [0-100]
• Exercises, mean ± SD [Min-Max]	72.8 ± 39 [0-100]	61.2 ± 39 [0-100]
Negative reactions to treatment		
• Medication, mean ± SD [Min-Max]	19.5 ± 33 [0-100]	23.6 ± 35 [0-100]
• Exercises, mean ± SD [Min-Max]	7.4 ± 19 [0-50]	26.2 ± 29 [0-100]
Perceived usefulness of treatments		
• Medication, mean ± SD [Min-Max]	66 ± 35 [0-100]	68 ± 30 [0-100]
• Exercises, mean ± SD [Min-Max]	60 ± 38 [0-100]	35 ± 21 [20-50]

SD: standard deviation, **n**: number, **Min**: minimum, **Max**: maximum

Multivariate analysis

In the multivariate analysis, the predictors of non-adherence according to the PARQ were advanced maternal age (p=0.004), low ESR (p=0.029), and negative reactions to medication (p<0.0001). For the CARQ, the only factor significantly associated with non-adherence was the difficulty in following the treatment regimen (p=0.042) as reported by the parent.

Table 3 summarizes the results of the univariate and multivariate analyses of factors influencing treatment adherence, as assessed by the PARQ and CARQ.

Table 3. Study of factors influencing therapeutic compliance according to PARQ and CARQ in uni- and multivariate analysis

	PARQ				**QARC**			
	Univariate analysis		**Multivariate analysis**		**Univariate analysis**		**Multivariate analysis**	
	p	r	p	B	p	r	p	B
Socio-demographic characteristics								
Patient age	0.101	-0.343			**0.036**	**-0.85**		
Patient gender	0.359				0.078			
Father's age	0.268	-0.241			0.561	-0.119		
Mother's age	**0.005**	**-0.572**	**0.004**	**-0.901**	**0.029**	**-0.421**		
Residential area	0.662				0.936			
Patient's educational status	0.845				0.366			
Father's educational level	0.984				0.555			
Mother's educational level	0.857				0.276			
Parental marital status	0.385				0.652			
Number of siblings	0.866	0.036			0.158	-0.265		
JIA Characteristics								
Age at JIA onset	0.668	0.092			0.981	0.005		
Disease duration	0.088	-0.356			**0.035**	**-0.386**		
JIA subtype	0.338				0.379			
Radiological profile	0.269				0.845			
Disease activity parameters								
VAS for pain	0.297	0.222			0.191	0.246		
PGA	0.336	0.205			0.724	0.067		
MS	0.498	0.145			0.552	0.113		
NA	0.487	-0.149			0.263	-0.211		
TJC	0.434	0.176			0.261	0.220		
SJC	0.636	0.107			0.710	0.074		
ESR	**0.001**	**0.643**	**0.029**	**0.390**	0.541	0.123		
CRP	**0.008**	**0.561**			0.201	0.259		
JADAS-10	0.558	0.132			0.665	-0.087		
Functional impact of JIA (C-HAQ)	0.618	0.153			0.406	0.216		
Therapeutic characteristics								
Number of csDMARDs prescribed	0.269	-0.275			0.348	0.205		
Type of csDMARDs used	0.054				0.325			
Duration of csDMARDs therapy	0.251	-0.285			0.353	-0.203		
Duration of cs and bDMARDs combination	0.846	0.082			0.475	-0.297		
Type of bDMARD used	0.137				0.308			
Duration of bDMARD therapy	0.769	0.124			0.165	-0.543		
Discontinuation of bDMARD	0.317	0.236			0.434	0.160	0.018	42.447
Number of NSAID tablets	0.541	0.316			0.582	0.255		
Number of corticosteroid tablets	0.817	-0.122			0.879	-0.065		
Parents' perception of treatment (PARQ)								
Difficulty with medication	**<0.0001**	**-0.698**			**0.001**	**-0.645**	**0.042**	**-0.601**
Difficulty with exercises	0.570	-0.295			0.791	0.124		
Negative reactions to medication	**0.001**	**-0.651**	**<0.0001**	**-0.599**	**0.011**	**-0.508**		
Negative reactions to exercises	0.587	-0.283			0.230	0.522		
Perceived usefulness of medication	0.370	0.191			0.851	0.040		
Perceived usefulness of exercises	0.014	0.949			0.215	0.671		
Patient perception of treatment (CARQ)								
Difficulty with medication	0.002	-0.593			**0.002**	**-0.552**		
Difficulty with exercises	0.721	0.167			0.824	-0.104		
Negative reactions to medication	**0.012**	**-0.506**			0.114	-0.294		
Negative reactions to exercises	0.334	-0.431			0.602	-0.219		
Perceived usefulness of medication	0.536	0.133			0.143	0.274		
Perceived usefulness of exercises	0.809	-0.113			0.336	-0.393		

VAS: visual analogue scale, **PGA**: patient's global assessment, **NA**: night awakenings, **MS**: morning stiffness, **TJC**: tender joint count, **SJC**: swollen joint count, **ESR**: erythrocytes sedimentation rate, **CRP**: C Reactive Protein, **C-HAQ**: Childhood Health assessment Questionnaire, **JADAS 10**: Juvenile Arthritis Disease Activity Score

Study of concordance between PARQ and CARQ results

The agreement analysis between the PARQ and CARQ items demonstrated a strong concordance for the "preferred treatment" category (κ = 0.659, p < 0.0001), with an overall agreement rate of 72%. This item also showed a significant, strong positive correlation (τb = 0.545, p = 0.001).
Conversely, the weakest agreement was observed for the "perceived usefulness of treatment" (κ = 0.194, p = 0.014), with an agreement rate of only 32%.
For the items "treatment responsibility," "treatment difficulty," and "treatment adherence," the concordance between PARQ and CARQ was moderate (k = 0.518, p=0.006; k = 0.439, p<0.0001; k = 0.415, p<0.0001, respectively).
These variables were also significantly and moderately associated (τb = 0.449, p=0.015; τb = 0.515, p=0.004; τb = 0.638, p<0.0001, respectively).
Regarding "negative reactions," the agreement between the two scores was weak (k = 0.286, p=0.002).

Discussion

In our study, 80% of parents reported that their children adhered to their prescribed treatments, aligning with a mean PARQ score of 74.58 ± 36 [0-100]. Similarly, 76.7% of patients self-reported adherence, corresponding to a mean CARQ score of 74 ± 34 [0-100]. Both scores were notably high, consistent with findings in the literature [9,10].
Medication adherence in JIA has been extensively studied, with compliance rates varying depending on the treatment type and assessment methods used. In the literature, adherence has primarily been evaluated using the PARQ and CARQ scores [9, 11-14], with reported compliance rates ranging from 72% to 88% for the PARQ and 74.8% to 84.45% for the CARQ [9, 11-14].
Discrepancies in adherence rates across studies using the same assessment tools may be attributed to several factors, including study duration, disease progression time, and, most importantly, the timing of adherence assessment—whether during treatment initiation or ongoing follow-up.
Alternative methods for evaluating adherence in JIA have also been explored. A recent Spanish study assessed adherence using the Medication Possession Ratio (MPR), reporting a rate of up to 96.3% [15]. This rate is notably higher than our findings, potentially due to the implementation of therapeutic education programs in Spain, which may enhance patient compliance.
Two studies conducted in Brazil assessed treatment adherence in JIA using the MORISKY questionnaire for parents and children over nine years of age. Reported adherence rates ranged from 46.5% to 69.2%, which were lower than those observed in our study [16,17]. A 2017 literature review reported a maximum adherence rate of 65% for biological treatments throughout the course of JIA [18].
Additionally, a recent Norwegian study evaluated adherence to csDMARDs and bDMARDs using the Morisky questionnaire 19 years after disease onset and found poor adherence in approximately half of the cases [19]. In contrast, a Brazilian pilot study using the PRAQ questionnaire reported good therapeutic adherence in 78.8% of cases [20].
In our study, fear of adverse effects was the primary reason for non-adherence, as reported by both patients and parents. Forgetfulness was cited by one child and one parent, while only one patient considered the treatment ineffective. Additionally, one parent identified delays in treatment reimbursement by the health insurance fund as a contributing factor to non-adherence. These findings align with existing literature, where fear of adverse effects is frequently reported as the leading cause of non-compliance among both patients and parents [11, 21, 22].
In contrast, a study by Juan Carlos Gonzales et al. identified disease remission as the primary reason for non-adherence (48.4%), followed by treatment ineffectiveness (29%), while fear of adverse effects was cited in only 12.9% of cases [15]. Similarly, Kearsley-Fleet et al. found that treatment inefficacy was the most common reason for treatment discontinuation (60%) [23], whereas De Civita et al. reported that forgetfulness was the primary factor in non-adherence (55%) [12]. Leslie et al. further demonstrated that pain intensity, as reported by both parents and children, significantly hindered medication adherence [10]. In contrast, Brandelli et al. suggested that fear of disease-related pain could actually promote better adherence to treatment [11].
A Canadian study published in 2019 identified two major factors affecting adherence: the absence of a parent on the day the medication was to be taken (41%) and patient reluctance toward injectable treatments (40%) [11]. Similarly, children's unwillingness to take medication was the leading cause of non-adherence in JIA, as highlighted in a meta-analysis by Santer et al. [24]. Additionally, Len et al. reported that an unstable family environment, such as parental separation or divorce, contributed to poor medication adherence [11,25]. Miotto et al. also demonstrated that unfavorable socioeconomic conditions were associated with higher rates of non-adherence [20].
Numerous studies have attempted to identify factors positively or negatively influencing adherence, yielding variable results. In our study, no association was found between female gender and treatment adherence. This finding is consistent with the results of De Civita et al. [12] but contrasts with those of Anne Lohse et al. and Miotto et al., who reported an association between female gender and poorer adherence [9,20].
Furthermore, in our study, PARQ and CARQ scores were strongly correlated with younger maternal age, a finding that contrasts with the results of De Civita et al. [12]. This may be explained by the fact that cognitive functions tend to decline with age, potentially leading to increased forgetfulness in managing a child's treatment [26].
PARQ and CARQ scores were not associated with JIA type, phenotypic or radiological disease profile, functional impairment, or the presence of coxitis or extra-articular manifestations, which is consistent with previous reports

in the literature [9]. However, a shorter disease duration was associated with higher CARQ scores, while elevated ESR and CRP levels were significantly correlated with higher PARQ scores. These findings suggest that longer disease duration may make adherence more challenging for the child, whereas higher disease activity (as reflected by increased ESR and CRP levels) may prompt parents to be more vigilant in ensuring medication adherence. These results contrast with previous studies, where no such associations between these parameters and medication adherence were identified [9,13]. Notably, in our study, no statistically significant relationship was observed between medication adherence (as assessed by PARQ and CARQ) and other disease activity parameters, a finding that aligns with a recent French study [9,13].

Regarding therapeutic characteristics, only the route of administration of bDMARDs was significantly associated with PARQ scores. However, several studies have reported a strong correlation between the type of bDMARD, particularly anti-TNF agents, and treatment adherence [27,28]. Additionally, Bugni et al. demonstrated that taking three or more tablets per day was strongly associated with poor adherence, a finding that contrasts with our results [29].

The analysis of agreement between the various PARQ and CARQ items demonstrated a strong concordance between the two questionnaires regarding the "best treatment," with an agreement rate of 72%. In contrast, the weakest agreement was observed for the "usefulness of treatment," with only 32% agreement. This finding is consistent with results from several other studies [9,13,30].

To the best of our knowledge, this is the first study conducted in Tunisia to evaluate treatment adherence in JIA. We utilized validated self-reported questionnaires, which demonstrated good reproducibility and were easily comprehensible for our patients. However, our study has certain limitations. Self-reported questionnaires remain inherently subjective and declarative, which may lead to an overestimation of adherence. Additionally, as this study was conducted in a single center with a relatively small sample size, the findings may not be generalizable to the broader population.

Conclusion

Our study demonstrated good therapeutic adherence among Tunisian patients with JIA. Factors associated with poor adherence included higher maternal age, lower disease activity, negative reactions to medication, and difficulties in following treatment. Identifying these factors and implementing targeted educational strategies for patients, their families, and healthcare professionals may improve adherence, thereby optimizing treatment efficacy and enhancing long-term patient outcomes.

Abbreviations:
ACPA: Anti-citrullinated peptide antibodies
ANA: Antinuclear antibodies
bDMARDs: Biologic disease modifying anti rheumatic drugs
CHAQ: Childhood Health Assessment Questionnaire
CARQ: Child Adherence Report Questionnaire
CI: Confidence intervals
CIR: Chronic inflammatory rheumatism
csDMARDs: Conventional synthetic modifying anti rheumatic drugs
ESR: Erythrocyte sedimentation rate
GPA: Global patient assessment
ICH: International Conference on Harmonization
ILAR: International League of Associations for Rheumatology
JADAS: Juvenile arthritis disease activity score
JIA: Juvenile Idiopathic Arthritis
MEA: Extra-articular manifestations
MS: Duration of morning stiffness
MTX: Methotrexate
NA: Number of night awakenings
PARC: Parent Adherence Report Questionnaire
PGA: Patient global assessment
RF: Rheumatoid factor
SJC: Swollen joint count
SPSS: Statistical Package for Social Science
SD: Standard deviation
TJC: Tender joint count
VAS: Visual analog scale

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