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# Efficacy and tolerance of a combination of corticosteroids and methotrexate in newly-diagnosed patients with juvenile dermatomyositis: a retrospective monocenter cohort study

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**Keywords:** juvenile dermatomyositis, methotrexate, paediatric rheumatology

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## Abstract

**Objectives:** To assess the efficacy and tolerance of the conventional first-line treatment by methotrexate (MTX) and corticosteroids (CS) in patients with juvenile dermatomyositis (JDM) regardless of severity.

**Methods:** We conducted a monocentric retrospective study of patients with newly-diagnosed JDM treated with MTX and CS from 2012 to 2020. Proportion of clinically inactive disease (CID) within six months of MTX initiation was evaluated using both PRINTO criteria (evaluating muscle inactive disease) and Disease Activity Score (evaluating skin inactive disease). We compared responders and non-responders using univariate analyses.

**Results:** Forty-five patients with JDM, out of which thirty (67%) severe JDM, were included. After six months of treatment with MTX and CS, complete CID, muscle CID and skin CID were achieved in 14/45 (31%), 19/45 (42%) and 15/45 (33%) patients respectively. The absence of myositis-specific (MSA) or myositis-associated autoantibodies (MAA) at diagnosis was associated with a better overall, cutaneous and muscular therapeutic response, compared to antibody-positive forms ( $p<0.01$ ). Requirement for ICU ( $p=0.029$ ) and cutaneous ulcerations ( $p=0.018$ ) were associated to a less favorable muscle response. MTX was stopped due to intolerance in six patients (13%) before month 6..

**Conclusion:** Conventional first-line treatment with MTX was not efficient in a large subset of JDM patients, especially in MSA and MAA-negative forms, and in patients with severe JDM. Larger multicenter cohorts are required to confirm these data and to identify new predictive biomarkers of MTX response, in order to treat patients with JDM as early as possible with appropriate targeted drugs.

***Key messages***

- Methotrexate resulted in clinically inactive disease in only 31% of newly-diagnosed juvenile dermatomyositis (JDM) patients.
- Methotrexate seems more efficient in JDM patients that are negative for muscle-specific/associated auto-antibodies than in antibody-positive forms.
- Muscle inactivity under methotrexate was achieved less often in severe patients than in the remaining patients.

Juvenile dermatomyositis (JDM) is a heterogeneous disease in respect of clinical phenotype, association with myositis-specific autoantibodies, histopathological stigmata and response to treatment. Following the results of one randomized trial [1], a combination of corticosteroids (CS) and methotrexate (MTX) is now recommended in patients with newly diagnosed JDM [2]. However, 28% of the patients assigned to this combination in the trial did not meet improvement criteria after a six-month treatment, and adverse events leading to MTX discontinuation occurred in 26% of cases. Moreover, the study excluded severe patients, and did not take into account the heterogeneity of JDM. In the present study, we aimed for the first time to assess the efficacy of the conventional first-line combination of CS and MTX at six months after treatment initiation in a cohort of newly-diagnosed JDM patients, regardless of disease severity

We retrospectively reviewed all patients with newly diagnosed JDM followed in the Paris referral center for Rare Paediatric Rheumatism and systemic autoimmune diseases (RAISE), who received a combination of MTX and CS between December 2012 and December 2020. Inclusion criteria were: i) diagnosis of JDM, according to conventional clinico-pathological criteria [3] with clinical muscle involvement, ii) first-line treatment with a combination of CS and oral or subcutaneous MTX and iii) follow-up of at least six months after the initiation of MTX. Patients who had previously received prednisone treatment alone during one month or less before MTX initiation were also included. Patients had a standardized assessment of skin, muscle and other organ involvement. Clinical and biological data were collected at disease onset and six months (M6) after treatment initiation. Muscle strength was assessed using the Childhood Myositis Assessment Scale (CMAS, range 0–52) and the Manual Muscle Testing (MMT) scale (range 0–80) [4] and skin disease activity using the skin Disease Activity Score tool (skin DAS, range 0–9) [5]. Severe JDM was defined by i) the requirement for intensive care unit (ICU), and/or ii) the presence of skin ulcerations and/or iii) the presence of a severe muscle involvement, defined by  $CMAS \leq 15$  or  $MMT \leq 30$ ,

and/or iv) the presence of a severe organ involvement: dysphonia and/or dysphagia, cardiac or pulmonary function impairment, gastrointestinal vasculitis occurring within the first month of diagnosis. Clinically inactive disease (CID) was defined by associating both the Paediatric Rheumatology International Trials Organisation (PRINTO) criteria for CID [6] (at least three out of four of the following: creatine kinase  $\leq 150$  U/L, CMAS  $\geq 48$ , MMT  $\geq 78$ , and Physician Visual Analogue Scale (VAS)  $\leq 0.2$ ), and inactive skin disease (skin DAS score  $\leq 1$  without skin ulcerations or erythema). Clinically inactive muscle and skin disease were respectively defined by CMAS  $\geq 48$  and MMT  $\geq 78$ , and skin-DAS  $\leq 1$  without ulcerations or erythema. The primary outcome was the proportion of patients achieving CID within the six months following the onset of MTX, without addition of another immunosuppressive treatment. We also assessed separately the achievement of muscle and skin CID, and the tolerance of MTX. Myositis-specific-antibodies (MSA) and myositis-associated antibodies (MAA) were assessed by dot-blot immunoassay using Euroline Autoimmune Inflammatory Myopathies 16 Ag (Euroimmun) and Blue Diver PMS12-24 (D-Tek). Muscle biopsies were centrally reviewed by one of the investigators (C.G.) using the validated score tool for muscle biopsy evaluation in patients with JDM [7]. All adverse events were recorded. Data were analyzed using descriptive statistics. Quantitative variables were described in terms of median with interquartile range (IQR), categorical variables as frequencies with percentages. Patients' characteristics at diagnosis were compared using chi-square or Fisher's exact test for discrete variables and Mann-Whitney U test for continuous variables. We conducted a univariate analysis to compare patients' characteristics at diagnosis according to the following endpoints at M6: CID, muscle-CID, skin-CID, and MTX intolerance leading to discontinuation before M6. A p-value less than 0.05 (two-sided) was considered statistically significant. Data was computed using the Medistica application software *p-value*. After parental consent, patients were registered in the French Centre des Maladies Rares (BAMARA). This study was approved by the Ethics board of Necker hospital.

Sixty-six patients diagnosed with JDM have been followed in our centre during the considered study period. Seventeen patients did not meet eligibility criteria (ten received another first-line treatment and seven had amyopathic JDM), and four were excluded due to missing data at M6. Thus, forty-five patients were included in analyses. Demographic, clinical, immunological and muscle pathological characteristics at diagnosis are shown in **Table 1**. Median age at diagnosis was 8.6 years (IQR 5.8-11.0). Dermatomyositis was classified as severe in thirty patients (67%), due to cutaneous ulcerations (16/45), severe muscle involvement (11/45), severe organ involvement (24/45) and/or requirement for ICU (6/45). Admissions to ICU were required because of swallowing difficulties (n=6), severe muscle involvement (n=5), and/or acute respiratory failure (n=2). Myositis-specific autoantibodies were found in thirty-one patients (69%), and MAA in four patients (9%). Muscle biopsy scores at diagnosis were available in twenty-two patients (49%), with a median overall histological score of 17.5 (IQR 12.2 – 20.0). Median delay between the first manifestation and the initiation of treatment was three months (IQR 1.6-5.6 months). Patients received initial treatment with a median daily dose of 1.5 milligram per kilogram of body weight per day (mg/kg/d) of prednisone (IQR 1.0-2.0) and a median weekly dose of 0.5 mg/kg of MTX (IQR 0.4-0.6). Twenty-three patients (51%) received methylprednisolone pulses. Methotrexate was administrated subcutaneously in thirty-six patients (80%) and orally in the remaining cases.

At M6, fourteen patients (31%) had achieved CID while on CS and MTX (complete responders). **Table 2** shows the comparison between complete responders (group 1) and non-responders and/or patients who were intolerant to MTX (group 2). There was no statistical difference between the two groups regarding gender, age at onset, diagnosis delay, clinical features at diagnosis, type of MSA, histological scores at diagnosis, and initial dosages and way of administration of CS and MTX. Univariate analyses showed that the proportion of patients without MSA or MAA and the muscle strength measured with MMT were

significantly higher in group 1 than in group 2. Conversely initial clinical manifestations and muscle biopsy scores did not significantly differ between the two groups.

When analysed separately, muscle and skin CID were achieved in nineteen patients (42%) and fifteen patients (33%) at M6 respectively. Patients who achieved muscle CID had higher median CMAS (35.0 *versus* 11.5,  $p=0.033$ ) and MMT scores (65.0 *versus* 50.0,  $p=0.033$ ) and less skin ulcerations at diagnosis (16% of patients *versus* 50%,  $p=0.018$ ) than patients who did not achieve muscle CID. None of the patients requiring ICU at disease onset achieved muscle CID under CS and MTX ( $p=0.029$ ). Patients who achieved skin CID had a lower initial skin DAS than patients who did not ( $p=0.033$ ), but the incidence of skin ulcerations did not significantly differ between the two groups (20% *versus* 37%,  $p = 0.12$ ). No difference was observed for histological scores.

Methotrexate was stopped in thirteen patients before M6 (29%), due to inefficacy (in nine patients) and/or to treatment intolerance (increase of transaminase levels or rash in six patients). None of these patients was hospitalized. Liver involvement at diagnosis (defined by elevated liver enzyme levels associated with elevated gamma-glutamyl transferase) was the only variable significantly associated with MTX intolerance ( $p < 0.01$ ).

In the present study, we found that less than a third of newly-diagnosed JDM patients achieved a CID with a first-line combination of CS and MTX in a tertiary pediatric rheumatology center. The proportion of patients who did not achieve remission at six months is much higher than what was observed in the clinical trial by *Ruperto et al.* [1], which reported a treatment failure only in 28% of the MTX group. However, the endpoint criteria, consisting in the PRINTO minimal improvement threshold [8] was less stringent than in our study. Moreover, it excluded severe patients with cutaneous or gastrointestinal ulceration, interstitial lung disease and/or cardiomyopathy, which represent 67 % of our cohort. Muscle CID was observed in a slightly higher number of patients (42%) than skin CID (33%) in our cohort study.



A recent study reported that around a quarter of patients with JDM still had active disease and damage two years after treatment initiation [9]. Chronic course is a major predictor of poor functional outcome in JDM [10]. Thus, the identification of biomarkers predictive of an early response to treatment represents a major unmet medical need in order to shorten the duration of active disease. Unique gene expression profiles in muscle biopsies from adult patients with MSA-defined subtypes of myositis suggests that different pathological mechanisms underlie muscle damage in each of these diseases, which may have therapeutic implications [11]. It has been shown that muscle pathology in combination with MSA is useful to predict the risk of remaining on treatment in JDM, and is associated with clinical severity and prognosis [12 13]. More recently, it was suggested that biomarker profiles could be used for predicting response to treatment in patients with JDM, since patients with high serum levels of galectin-9, CXCL10, TNFR-2, and galectin-1 may respond sub-optimally to conventional treatment [14]. An important group of investigated biomarkers is related to the type 1-IFN signature, which has been demonstrated in the peripheral blood and muscle biopsies of JDM patients [15]. So far, IFN $\alpha$ 2 protein measurements obtained by SIMOA have been shown to correlate with disease activity, but it has not been evaluated as a possible predictor of treatment response [16]. Herein we show for the first time that the absence of detectable MSA or MAA at diagnosis was associated with a better overall, cutaneous and muscular therapeutic response to MTX. Interestingly, none of the patients who required an admission to ICU achieved muscle CID at M6 under MTX. Cutaneous ulcerations, which result from skin vasculopathy, were also associated with a less favourable muscle outcome. This finding confirms that severe vasculopathy-related clinical features could be associated with severe JDM refractory to MTX [13, 17]. Conversely, we did not find a significant association between the vascular histological score domain and therapeutic response, but this result should be interpreted with caution since muscle biopsy data was only available in 49% of the patients. Altogether, these features emphasize the high heterogeneity

of JDM and the need for tailoring the first-line treatment according to each subtype of JDM. Besides MTX which remains efficient in the treatment of a large subset of JDM without criteria of severity, Janus-kinase inhibitors seem to be a potential promising first line treatment, especially in a subset of severe anti-NXP2 and anti-MDA5 positive JDM patients [18].

MTX intolerance is a frequent unwanted side effect and the most common reason for treatment discontinuation in juvenile inflammatory diseases, occurring for example in 25% of patients with juvenile idiopathic arthritis within six months of MTX treatment [19]. Intolerance to MTX leading to treatment discontinuation occurred in 13% of patients in our cohort, which was lower than in the *Ruperto et al.* study.

Our study has several limitations. The monocentric design restricted the number of included patients, which was notably too small to conduct multivariate analyses. However, the use of the same medical team guaranteed continuity of follow-up and homogeneity in treatment protocols.

In conclusion, this study emphasizes that the conventional first-line treatment with MTX is not efficient in a large subset of JDM patients, especially in patients with MSA-positive forms, and in patients with severe JDM. Larger multicenter cohorts are required to confirm these data and to identify new biomarkers predictive of response to MTX, in order to treat patients with JDM as early as possible with appropriate targeted drugs.

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**Conflict of Interest:** The authors have no conflicts of interest to disclose.

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**Table 1:** Baseline demographic, clinical, biological, pathological and treatment characteristics in 45 JDM patients

Baseline characteristics	<i>N</i> = 45
Female / male ratio	29 / 16
Median time from symptoms to JDM diagnosis, months (IQR)	3,0 (1,6 – 5,6)
Median age at diagnosis, years (IQR)	8,6 (5,8 – 11,0)
Skin-DAS [0-9], (IQR)	6,0 (5,0 – 7,0)
Malar rash, n (%)	25 (56)
Telangiectasia (cutaneous, periungueal and/or gingival), n (%)	26 (58)
Gotttron's papule, n (%)	27 (60)
Poikiloderma, n (%)	9 (20)
Livedo, n (%)	11 (24)
CMAS [0-52], (IQR)	21,0 (7,0 – 41,0)
MMT [0-80], (IQR)	55,0 (44,8 – 68,8)
Creatine kinase rate [N<150], U/L (IQR)	647,5 (173,5 – 3784,0)
Arthritis/arthritis, n (%)	6 (13)
Liver involvement, n (%)	9 (20)
Severe JDM, n (%)	30 (67)
- Requirement for ICU, n (%)	6 (13)
- Dysphonia/dysphagia, n (%)	15 (33)
- Gastrointestinal vasculitis, n (%)	10 (22)
- Pulmonary involvement, n(%)	10 (22)
- Cardiomyopathy, n(%)	2 (4)
- Cutaneous ulcerations, n (%)	16 (36)
- Severe muscle involvement, n (%)	11 (24)
<i>Number of muscle biopsies</i>	<i>n</i> = 31
Total muscle biopsy score (IQR)	17.5 (12.2 – 20.0)
- Inflammatory (IQR)	8 (6.0 – 10.8)
- Muscle fiber (IQR)	6.5, IQ 5.0 – 9.8)
- Vasculopathy (IQR)	1.5 (1.0 – 2.0)
- Connective lesions (IQR)	1 (0 – 1.8)
MSA, n (%)	31 (69)
TIF1γ / NXP2 / MDA5 / SAE (n)	11 / 11 / 8 / 1
MAA, n (%)	4 (9)
Ku / SSA / RNP	2 / 1 / 1
No MSA, no MAA, n (%)	12 (27)
<i>Treatment</i>	
Median time from JDM onset to CS initiation, months (IQR)	3.0 (1.5 – 6.6)
Methylprednisolone pulses at diagnosis, n (%)	23 (51)
Intravenous CS treatment (excluding pulses), n (%)	1.5 (1.0 – 2.0)
Initial daily CS dose, mg/kg (IQR)	36 (80)
Subcutaneous methotrexate use, n (%)	0.5 (0.4 – 0.6)
Weekly methotrexate dose, mg/kg (IQR)	

Data are presented as median (IQR) or number of patients (%). CMAS: Childhood Myositis Assessment Scale, CS: corticosteroids, DAS: disease activity scale, ICU: intensive care unit, , MAA:

Myositis-Associated Antibodies, MMT: Manual Muscle Testing, MSA: Myositis-Specific Antibodies, VAS: Visual Assessment Scale.

**Table 2:** Baseline demographic, clinical, biological, pathological and treatment characteristics in patients who achieved CID (group 1) and who did not achieve CID (group 2) at M6.

Baseline characteristics	Group 1 n = 14	Group 2 n = 31	p-value
Female / male ratio	10 / 4	19 / 12	0.74
Median time from symptoms to JDM diagnosis, months (IQR)	3.6 (2.0 – 7.9)	3.0 (1.4 – 5.0)	0.18
Median age at diagnosis, years (IQR)	10.3 (7.9 – 11.0)	8.3 (5.1 – 11.1)	0.27
Skin DAS [0-9], (IQR)	6.0 (4.3 – 6.0)	6.0 (5.0 – 7.0)	0.11
Malar rash, n (%)	8 (57)	17 (55)	0.89
Telangiectasia (cutaneous, periungueal and/or gingival), n (%)	7 (50)	19 (61)	0.48
Gotttron's papule, n (%)	8 (57)	19 (61)	0.79
Poikiloderma, n (%)	1 (7)	8 (26)	0.23
Livedo, n (%)	3 (21)	8 (26)	0.99
CMAS [0-52], (IQR)	35.0 (22.8 – 42.5)	18.0 (6.0 – 34.5)	0.11
MMT [0-80], (IQR)	67.5 (58.5 – 75.3)	50.0 (41.0 – 62.3)	0.05
Creatine kinase rate [N<150], U/L	552.0 (248.0 – 3307.5)	1000.0 (160.0 – 3906.0)	0.94
Arthritis/arthralgia, n (%)	2 (4)	4 (13)	0.90
Liver involvement, n (%)	2 (4)	7 (23)	0.52
Severe JDM, n (%)	10 (71)	20 (65)	0.74
Requirement for ICU, n (%)	0 (0)	6 (19)	0.15
Dysphonia/dysphagia, n (%)	5 (36)	10 (32)	0.99
Gastrointestinal vasculitis, n (%)	2 (14)	8 (26)	0.47
Pulmonary involvement, n (%)	2 (14)	8 (26)	0.47
Cardiomyopathy, n (%)	0 (0)	2 (6)	0.99
Severe muscle involvement, n (%)	2 (14)	9 (29)	0.46
Cutaneous ulcerations, n (%)	3 (21)	13 (42)	0.31
<i>Number of muscle biopsies</i>	<i>n = 7</i>	<i>n = 15</i>	
Total biopsy score (IQR)	17.0 (14.5 – 23.5)	18.0 (7.0 – 20.0)	0.46
- Inflammatory (IQR)	8.0 (7.0 – 11.5)	8.0 (3.0 – 9.5)	0.23
- Muscle fiber (IQR)	6.0 (5.0 – 9.0)	7.0 (3.0 – 9.5)	0.67
- Vasculopathy (IQR)	1.0 (1.0 – 2.0)	0 (0 – 1.0)	0.71
- Connective lesions (IQR)	2.0 (0.5 – 2.0)	0 (0 – 1.0)	0.1
<i>MSA, n (%)</i>			
- TIF1γ	2 (14)	9 (29)	0.46
- NXP2	3 (21)	8 (26)	0.99
- MDA5	1 (7)	7 (23)	0.40
- SAE	0 (0)	1 (3)	0.99
<i>MAA, n (%)</i>			
- Anti-Ku	0 (0)	2 (6)	0.99
- Anti-SSA	0 (0)	1 (3)	0.99
- Anti-RNP	0 (0)	1 (3)	0.99
<i>No MSA, no MAA</i>	8 (57)	3 (10)	<0.01
<i>Treatment</i>			
Median time from JDM onset to CS initiation, months (IQR)	4.1 (2.0 – 7.9)	3.0 (1.4 – 9.0)	0.26
Methylprednisolone pulses, n (%)	7 (50)	16 (52)	0.84
Intravenous CS treatment, excluding pulses, n (%)	7 (50)	14 (45)	0.84
Initial daily CS dose, mg/kg (IQR)	2.0 (1.5 – 2.0)	1.5 (1.0 – 2.0)	0.2

Subcutaneous methotrexate use, n (%)	9 (64)	27 (87)	0.09
Weekly methotrexate dose, mg/kg (IQR)	0.4 (0.3 – 0.4)	0.4 (0.4 – 0.6)	0.06

Data are presented as median (IQR) or number of patients (%). CMAS: Childhood Myositis Assessment Scale, CS: corticosteroids, DAS: disease activity scale, ICU: intensive care unit, IQR: interquartile range, MAA: Myositis-Associated Antibodies, MMT: Manual Muscle Testing, MSA: Myositis-Specific Antibodies, VAS: Visual Assessment Scale.