Paediatric rheumatology

Comparison of clinical features and drug therapies among European and Latin American patients with juvenile dermatomyositis

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Abstract

Objective

To compare the demographic features, presenting manifestations, diagnostic investigations, disease course, and drug therapies of children with juvenile dermatomyositis (JDM) followed in Europe and Latin America.

Methods

Patients were inception cohorts seen between 1980 and 2004 in 27 paediatric rheumatology centres. The following information was collected through the review of patient charts: sex; age at disease onset; date of disease onset and diagnosis; onset type; presenting clinical features; diagnostic investigations; course type; and medications received during disease course.

Results

Four hundred and ninety patients (65.5% females, mean onset age 7.0 years, mean disease duration 7.7 years) were included. Disease presentation was acute or insidious in 57.1% and 42.9% of the patients, respectively. The course type was monophasic in 41.3% of patients and chronic polycyclic or continuous in 58.6% of patients. The more common presenting manifestations were muscle weakness (84.9%), Gottron’s papules (72.9%), heliotrope rash (62%), and malar rash (56.7%). Overall, the demographic and clinical features of the 2 continental cohorts were comparable. European patients received more frequently high-dose intravenous methylprednisolone, cyclosporine, cyclophosphamide, and azathioprine, while methotrexate and antimalarial medications were used more commonly by Latin American physicians.

Conclusion

The demographic and clinical characteristics of JDM are similar in European and Latin American patients. We found, however, several differences in the use of medications between European and Latin American paediatric rheumatologists.

Key words

juvenile dermatomyositis, onset manifestations, clinical features, disease course, drug therapy

Introduction

Juvenile dermatomyositis (JDM) is a multisystem vasculopathic disease of presumed autoimmune etiology that involves primarily the skin and muscles. Other organs may be affected, including the gastrointestinal tract, heart and lungs, and, more rarely, the kidneys, eyes, and central nervous system (1-3). The onset of JDM is quite variable, with some patients experiencing the insidious development of progressive muscle weakness and skin rash, and others having a more acute onset with fever, profound muscle weakness, widespread cutaneous manifestations, and occasionally ulcerative lesions. The disease course is also heterogeneous. It may range from a monophasic course, with good response to treatment and full recovery within 2 years after diagnosis without relapse, to a chronic polycyclic or continuous course, with relapsing-remitting or persistently active disease for longer than 2 years after diagnosis and a significant risk of development of disease-related complications (1).

Prior to the introduction of corticosteroids in the 1960s for treatment of the disease, almost one-third of patients with JDM died, one-third were left with permanent disabilities, and only one-third recovered without complications (4). Since then, the mortality has decreased to less than 2%, and there has been a considerable improvement in functional outcome. However, many patients are refractory or respond suboptimally to current treatments and are at risk of developing irreversible damage from the disease activity or its treatment (5-7). This morbidity may have a serious impact on the quality of life of patients and their family. Recent improvement in patient outcomes is largely due to the refinement in protocols of corticosteroid administration, including the use of high-dose intravenous methylprednisolone pulses, and to the introduction of second-line medications, such as methotrexate, cyclosporine, and intravenous immunoglobulin (8-10). However, there have been no randomised controlled trials of any medications in children with JDM. Consequently, disease management remains largely empirical and based on observational studies and clinical experience.

A number of studies have described the clinical features and treatment modalities of series of patients with JDM (1, 3, 11, 12, 13). However, most studies come from single centres or are small. We recently collected a large sample of children with JDM in the context a multinational, multicenter study, whose primary aims were to investigate the long-term outcome of the disease and to search for prognostic factors. This study provided the opportunity to compare patient populations followed in paediatric rheumatology centres in different continents, namely Europe and Latin America. The results of outcome analysis have been reported previously (7). In this paper, we present the data regarding demographic features, presenting manifestations, diagnostic investigations, disease course, and use of drug therapies.

Patients and methods

Study design and patient selection

The study protocol was described in detail elsewhere (7). Briefly, investigators in each participating centre were first asked to identify all patients seen between January 1980 and December 2004 who had a diagnosis of JDM by Bohan and Peter’s criteria (14, 15), were age <18 years at disease onset, and had at least 24 months of disease (i.e. follow-up) duration between disease onset and the time of last follow-up observation. Next, each investigator was asked to collect retrospective data and to assess cumulative damage through the review of clinical data from disease onset to last follow-up visit or, if the patient had died, to the last visit before death. Investigators were also asked to make the cross-sectional assessment of all patients who were still followed or were no longer followed and were alive. Informed consent to participate in the study was provided by both the parent/guardian and the patient (when applicable). Ethics committee approval of the study was obtained in all participating countries. Outcome data were collected between 2003 and 2006.
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**Retrospective assessment**

The following information was collected through the review of patient charts: sex; age at disease onset; date of disease onset and diagnosis (as recorded by the attending physician); onset type (acute: with high fever, prostration, prominent rash or profound muscle weakness, or insidious: progressive development of muscle weakness and rash); presenting clinical features (clinical manifestations observed in the first month of illness); diagnostic investigations (electromyography and muscle biopsy); course type, not including being off medications (monocyclic: full recovery within 2 years after diagnosis without relapse, chronic polycyclic: relapsing-remitting disease, or chronic continuous: persistently active disease for longer than 2 years after diagnosis) (16-18); and medications received during the disease course.

**Damage assessment and cross-sectional evaluation**

The methodology used for these assessments and the results obtained were reported elsewhere (7). Briefly, cumulative damage was assessed with the Myositis Damage Index (MDI) (19). This tool assesses the extent of damage in the muscle, skeletal, cutaneous, gastrointestinal, pulmonary, cardiac, peripheral vascular, endocrine, ocular, infectious, malignancy, and other organ/systems. The following clinical assessments were performed at cross-sectional visit: muscle strength and function/endurance through the 8-muscle Kendall Manual Muscle Testing (MMT) (20) and the Childhood Myositis Assessment Scale (CMAS) (21), respectively; overall disease activity through the Disease Activity Score (DAS) (22) and the Myositis Disease Activity Assessment VAS (MYOACT) (13); physical function through the Childhood Health Assessment Questionnaire (CHAQ) (23, 24); HRQL through the parent version of the Child Health Questionnaire (CHQ) (24, 25); satisfaction with illness outcome (very satisfied, moderately satisfied or not satisfied).

**Statistics**

Comparison of features between European and Latin American patients was made by means of the Mann-Whitney U-test in case of continuous variables and of chi-square or the Fisher exact test, as appropriate, in case of categorical data. Bonferroni adjustment was applied as a correction for multiple comparisons to explore post-hoc differences between pairs of patients groups. The separate (univariate) and joint (multivariate) effects of predictor variables on long-term outcomes were examined. Predictor variables were sex, continent, ethnicity, and year of onset, onset age, onset type, onset manifestations, course type, disease duration and duration of active disease. Outcomes were muscle strength/endurance, continued disease activity, cumulative damage, muscle damage, cutaneous damage, calcinosis, lipodystrophy, physical function, and HRQL. Bivariate analyses were first made for each outcome. Then, multiple logistic regression analyses were carried out entering predictor variables as explanatory variables and each disease outcome as outcome variable. Cases with missing data were excluded. Variables that were significantly associated with the outcome in bivariate analyses were entered in multivariate procedures. Using a backward selection procedure, predictor variables that were significantly associated with the outcome were identified. The effect was expressed in terms of the odd ratios.

### Table I. Main demographic and clinical features and diagnostic procedures features in 490 children with juvenile dermatomyositis.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=490)</th>
<th>Europe (n=248)</th>
<th>Latin America (n=242)</th>
<th>p-value&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, no. (%)</td>
<td>490 321 (65.5)</td>
<td>248 169 (68.1)</td>
<td>242 152 (62.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Mean (SD) age at disease onset, years</td>
<td>486 7.0 (3.7)</td>
<td>247 6.9 (3.7)</td>
<td>239 7.0 (3.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age at disease onset, no. (%)</td>
<td>486</td>
<td>247</td>
<td>239</td>
<td>0.99</td>
</tr>
<tr>
<td>≤5 years</td>
<td>127 (35.4)</td>
<td>88 (35.6)</td>
<td>44 (35.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>5-10 years</td>
<td>211 (43.4)</td>
<td>107 (43.5)</td>
<td>104 (43.5)</td>
<td>0.80</td>
</tr>
<tr>
<td>10-18 years</td>
<td>103 (21.2)</td>
<td>52 (21.1)</td>
<td>51 (21.3)</td>
<td>0.80</td>
</tr>
<tr>
<td>Year of disease onset, no. (%)</td>
<td>487</td>
<td>248</td>
<td>239</td>
<td>0.80</td>
</tr>
<tr>
<td>1980-1990</td>
<td>98 (20.1)</td>
<td>47 (19.0)</td>
<td>51 (21.3)</td>
<td>0.80</td>
</tr>
<tr>
<td>1991-2000</td>
<td>280 (57.5)</td>
<td>145 (58.5)</td>
<td>135 (56.5)</td>
<td>0.80</td>
</tr>
<tr>
<td>2001-2004</td>
<td>109 (22.4)</td>
<td>56 (22.6)</td>
<td>53 (22.2)</td>
<td>0.80</td>
</tr>
<tr>
<td>Mean (SD) time lag between disease onset and diagnosis, years</td>
<td>474 0.6 (1.0)</td>
<td>241 0.6 (1.1)</td>
<td>233 0.6 (0.9)</td>
<td>0.02&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Onset type, no. (%)</td>
<td>475 242</td>
<td>233</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>271 (57.1)</td>
<td>147 (60.7)</td>
<td>124 (53.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Insidious</td>
<td>204 (42.9)</td>
<td>95 (39.3)</td>
<td>109 (46.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Patients who underwent electromyography, no. (%)</td>
<td>479 287 (59.9)</td>
<td>153 (62.7)</td>
<td>134 (57.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Patients with normal findings</td>
<td>264 (55.1)</td>
<td>141 (57.8)</td>
<td>123 (52.3)</td>
<td>0.90</td>
</tr>
<tr>
<td>Patients with normal findings</td>
<td>23 (4.8)</td>
<td>12 (4.9)</td>
<td>11 (4.7)</td>
<td>0.82</td>
</tr>
<tr>
<td>Patients who underwent muscle biopsy, no (%)</td>
<td>469 259 (55.2)</td>
<td>136 (55.7)</td>
<td>123 (54.7)</td>
<td>0.20</td>
</tr>
<tr>
<td>Patients who underwent needle biopsy</td>
<td>63 (13.4)</td>
<td>38 (15.6)</td>
<td>25 (11.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Patients who underwent surgical biopsy</td>
<td>196 (41.8)</td>
<td>98 (40.2)</td>
<td>98 (43.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Course type, no. (%)</td>
<td>479 247</td>
<td>232</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Monophasic</td>
<td>198 (41.3)</td>
<td>97 (39.3)</td>
<td>101 (43.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Chronic polycyclic or continuous</td>
<td>281 (58.6)</td>
<td>150 (60.8)</td>
<td>131 (56.5)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

<sup>+</sup>Europe versus Latin America. SD: standard deviation. P-values refer to the chi-square test unless otherwise specified. *Mann-Whitney U-test.
Results

Six hundred and six patients were identified at 27 paediatric rheumatology centres in 5 countries (Argentina, Brazil, Italy, Mexico, and the United Kingdom). Fifty-four patients (8.9%) were excluded because the clinical chart could not be retrieved and 62 patients (10.2%) were excluded because they had a disease onset before 1980 or a follow-up duration <2 years or undefined. The remaining 490 patients, including 15 (3.1%) who had died, were included in the study. Of them, 248 (50.6%) were enrolled in Europe (168 in Italy and 80 in the United Kingdom), and 242 (49.4%) were enrolled in Latin America (117 in Brazil, 75 in Argentina and 50 in Mexico).

Table I shows the main demographic features of the study patients, considered as whole and by continent. Overall, two-thirds of patients were female and the mean age at disease onset was 7.0 years. The mean disease duration between disease onset and last follow-up visit or death was 7.7 years (range 2–25.2 years). Onset was most common between age 5–10 years and least common after age 10 years. Around one-third of patients were age <5 years at disease onset. There was a relatively greater prevalence of females in patients with onset between 5 and 10 years of age (71.1%) than in those with onset before 5 years (60.5%) or after 10 years (63.1%), but the difference was not significant. More than half patients had disease onset in the decade 1991–2000, whereas the percentage of patients who had disease onset between 1980 and 1990 and between 2001 and 2004 was comparable (around 20%).

Gender ratio, age at disease onset and distribution of onset across decades were comparable between the 2 continental cohorts. European patients had a slightly longer time lag between disease onset and disease diagnosis than did Latin American patients. The age at onset for girls and boys is depicted in Figure 1. There was a peak age at 5 years for girls, whereas no definite peak age was seen for boys. Girls outnumbered boys at all ages, except at ages 12 and 15. The relative prevalence of females was more marked between ages 7 and 11 years. Overall, disease onset was less common after 11 years of age.

The disease characteristics, diagnostic investigations, and disease course are also presented in Table I. Disease presentation was recorded as being more frequently acute than insidious. Around 60% of patients underwent electromyography, which was abnormal in more than 90% of instances. Muscle biopsy was performed in 55.2% of patients, 75.7% of whom had the investigation performed surgically. Histological evaluation of muscle biopsy samples was pathologic in 88.6% of instances. The disease course was monophasic in 41.3% of patients and chronic polycyclic or continuous in 58.6% of patients. There were no differences in any of these features between European and Latin American patients.

The main clinical manifestations observed at disease onset in the whole patient sample were, in order of frequency, muscle weakness (84.9%), Gottron’s papules (72.9%), heliotrope rash (62%), malar rash (56.7%), arthritis (35.7%), fever (30.8%), dysphagia (17.8%), dysphonia (11.4%), skin ulcers (6.3%), Raynaud phenomenon (5.3%), calcinosis (3.7%), and intestinal vasculitis (0.2%). The frequency of presenting manifestations was comparable between the 2 continental cohorts, with the exception of malar rash and dysphonia, which were seen more commonly in European patients, and Gottron’s papules, which were more frequent in Latin America patients (Fig. 2).

Table II shows the frequency of presenting clinical manifestations by age at disease onset. All clinical manifestations were comparable across onset age groups, with the exception of a greater frequency of dysphagia in older children. Analysis of predictors of long-term outcome showed that cutaneous manifestations at onset were protective for decreased muscle function on the CMAS, but predicted continued disease activity on the MYOACT. Children who presented with dysphagia or dysphonia were more likely to have decreased muscle function on the CMAS. Muscle weakness at onset was associated with long-term muscle damage (7).

The medications administered during the disease course were, in order of frequency, corticosteroids (98.5%), methotrexate (56.2%), high-dose (pulse) intravenous methylprednisolone (41.7%), antimalarials (32.4%), cyclosporine (25.5%), intravenous immunoglobulin (17.2%), cyclophosphamide (10.1%), bisphosphonates (10.0%), azathioprine (9.8%), and biologic medications (2.7%). The comparison of drug therapies between European and Latin American patients is illustrated in Figure 3. European patients had received more frequently high-dose intravenous...
methylprednisolone, cyclosporine, cyclophosphamide, and azathioprine, whereas methotrexate and antimalarials medications were used more frequently by Latin American paediatric rheumatologists. Intravenous immunoglobulins were administered with equal frequency in the 2 continental populations.

Table III reports the frequency of prescribed medications by decade of disease onset. Although corticosteroid therapy was given to nearly all patients seen throughout decades, use of high-dose intravenous methylprednisolone became more popular in the 90s and 2000s. Methotrexate administration increased sharply over the years, with patients seen in the 2000s being almost three times more likely to have received this drug than did those seen in the 80s. Cyclosporine, intravenous immunoglobulin, and antimalarials were given more frequently in the 90s than in the 80s, but their use remained stable thereafter. Prescription of azathioprine tended to decline over the years, whereas cyclophosphamide was used with similar frequency across decades. However, administration of cyclophosphamide was marked by a progressive decline in the use of the oral route and by a relative increase in the choice of the intravenous pulse regimen in the 2000s.

Methylprednisolone pulses were found to be protective toward the development of global and muscle damage. Therapy with intravenous immunoglobulin methotrexate, and cyclophosphamide was associated with continued muscle weakness, ongoing disease activity, long-term damage, and worse functional outcome (results not shown). However, this association is likely explained by patients with more severe disease being more likely to have received such treatments.

Discussion

We evaluated the demographic and clinical features, diagnostic procedures, and frequency of medication use in 490 children with JDM seen over a 25-year period in 27 paediatric rheumatology centres in 2 continents, Europe and Latin America. The female-to-male ratio (2:1) and the average age at disease onset (7.0 years) seen in our patients are similar to those reported...
in previous studies (1, 2). The greater frequency of disease onset in the 5-to-10-year old range is consistent with the peak onset age reported in previous studies (26). The proportion of children with disease onset before 4 years of age in our cohort (25.7%) is comparable to that found by Pachman and co-workers (25%) (27). Demographic features were remarkably similar in the 2 continental cohorts, indicating that the paediatric age group targeted by the disease is the same in different ethnic groups or geographic areas.

As expected, proximal muscle weakness and the characteristic skin rashes were the most common presenting features in the large majority of our children with JDM. The frequency of onset manifestations observed in the study sample is in the range of that reported in other series of JDM patients (1, 12, 28-30). The frequency of presenting symptoms was comparable between European and Latin American patients, with the sole exception a greater frequency of malar rash and dysphonia in European patients and of Gottron’s papules in the Latin American population. Presenting features were also similarly distributed across different onset age groups, although dysphagia was reported more frequently in patients with onset after 10 years of age (perhaps owing to the greater capacity of older children to self report this complaint).

These findings suggest that the clinical spectrum of JDM is similar in different geographic or ethnic groups and is not influenced by age at disease onset. Although the presentation of JDM is variable, it is seen that onset is usually insidious, with development of progressive muscle weakness and pain; a more acute onset, with fever, prostration and profound muscle weakness occurs in approximately one third of children (1). In our population, acute onset was recorded more frequently than insidious onset, with both continental samples revealing the same trend. Our findings should be regarded with caution, however, due to the difficulty in ascertaining the severity and acuteness of disease presentation in a retrospective analysis.

Earlier studies showed that 15–25% of JDM patients had a monophasic course, with the remaining patients demonstrating a chronic course with either flares or unremitting disease activity (16, 17). The more recent analyses have reported a greater proportion of patients with monophasic course (37–40%) (5, 18), which is comparable to that found in our study (41.3%). The increase over time in the proportion of JDM patients with milder disease course may reflect the recognition of the importance of prompt aggressive therapy with high-dose corticosteroids after the 1980s. The detection of the typical myopathic abnormalities on electromyography and the demonstration of the characteristic pathological changes on muscle biopsy are still the mainstay diagnostic procedure for JDM. They are part of the Bohan and Peter criteria used to diagnose JDM (14, 15). However, it has become clear that few clinicians subject children to the full work-up that would be required to fulfil the Bohan and Peter criteria. A recent international survey has shown that only 56% of paediatric rheumatologists used electromyography, and only 61% used muscle biopsy to diagnose JDM (31). Likewise, only 59.9% and 55.2% of our patients underwent electromyography or muscle biopsy, respectively.

Our analysis provided the opportunity to compare the medications used in the treatment of children with JDM by paediatric rheumatologists working in different areas of the world and to examine the trend in therapeutic choices throughout decades. As expected, nearly all patients in both continental cohorts were given corticosteroids during

### Table III. Medication choices by decade. Data are number (percentage).

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<tbody>
<tr>
<td>Corticosteroids</td>
<td>93 (98.9)</td>
<td>274 (98.9)</td>
<td>105 (97.2)</td>
<td>0.51a</td>
<td>1980-1990 vs. 1991-2000, 1991-2000 vs. 2001-2004</td>
</tr>
<tr>
<td>Intravenous methylprednisolone pulses</td>
<td>26 (27.7)</td>
<td>120 (43.3)</td>
<td>54 (50.0)</td>
<td>0.004</td>
<td>1980-1990 vs. 1991-2000</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>27 (28.7)</td>
<td>153 (55.2)</td>
<td>89 (82.4)</td>
<td>&lt;0.0001</td>
<td>1980-1990 vs. 1991-2000, 1991-2000 vs. 2001-2004</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>10 (10.6)</td>
<td>85 (30.7)</td>
<td>28 (25.9)</td>
<td>0.0006</td>
<td>1980-1990 vs. 1991-2000</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>6 (6.4)</td>
<td>55 (19.9)</td>
<td>22 (20.4)</td>
<td>0.007</td>
<td>1980-1990 vs. 1991-2000</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>22 (23.4)</td>
<td>92 (33.2)</td>
<td>42 (38.9)</td>
<td>0.06</td>
<td>1980-1990 vs. 1991-2000</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>14 (14.9)</td>
<td>25 (9.0)</td>
<td>8 (7.4)</td>
<td>0.16</td>
<td>1980-1990 vs. 1991-2000</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>12 (12.8)</td>
<td>21 (7.6)</td>
<td>15 (13.9)</td>
<td>0.11</td>
<td>1980-1990 vs. 1991-2000</td>
</tr>
<tr>
<td>Oral cyclophosphamide</td>
<td>10 (10.6)</td>
<td>7 (2.5)</td>
<td>1 (0.9)</td>
<td>0.001a</td>
<td>1980-1990 vs. 1991-2000</td>
</tr>
<tr>
<td>Intravenous cyclophosphamide pulses</td>
<td>3 (3.2)</td>
<td>14 (5.1)</td>
<td>14 (13.0)</td>
<td>0.006</td>
<td>1980-1990 vs. 1991-2000, 1991-2000 vs. 2001-2004</td>
</tr>
</tbody>
</table>

*p-values refer to the chi-square test unless otherwise specified. *Fisher’s exact test. *Pairs of comparisons that are statistically significant after Bonferroni correction for multiple comparisons.
their disease course. However, Euro-
pean physicians used more frequently
high-dose intravenous methylpred-
nisolone, cyclosporine, cyclophospha-
mide, and azathioprine, whereas Latin
American physicians were more likely
to prescribe methotrexate and antima-
larial drugs. These differences are un-
likely to depend on diversities in dis-
ease manifestations as the frequency of
presenting features of the 2 continental
populations was comparable. A recent
survey of treatment in JDM among
North American paediatric rheumatol-
ist showed considerable variation in the
choice of medications and the doses
administered (32). These observations
reflect the lack of data on which to base
treatment decisions.

We found a remarkable change over
time in the frequency of use of medica-
tions or therapeutic protocols. As com-
pared to the 80s, there was a significant
increase after the 90s in the frequency
of administration of high-dose (pulse)
intravenous methylprednisolone and
second-line drugs, namely methotrex-
ate, cyclosporine, and intravenous im-
munoglobulin. This reflects the recent
shift toward early aggressive treatment of
JDM, aimed to achieve rapid and
sustained remission and to prevent dis-
ease- and treatment-related complica-
tions (2, 8, 33, 34).

Although the increase in the frequency
of use of antimalarial agents across
decades was not significant, these med-
ications were prescribed to as many as
39% of patients managed in the 2000s.
This suggests that antimalarial drugs,
particularly hydroxychloroquine, re-
main popular for the treatment of skin
manifestations of JDM, which is the
indication for which they were initially
proposed (35). Use of azathioprine was
found to decline over time, whereas cy-
clophosphamide was still administered
to a sizable proportion of patients seen
in the current decade, particularly in
Europe. This drug was likely used in
patients with severe, refractory disease,
particularly those with the most seri-
ous complications (36). Administra-
tion of cyclophosphamide through the
oral route was almost abandoned in
the 2000s, whereas the regimen based on
intravenous pulse infusions became in-
creasingly more popular over time. This
may reflect the notion that intravenous
pulse regimens lead to a lesser toxici-
ty than does oral daily administration
(37). Only a few patients received the
novel biologic medications, reflecting
the still limited experience with these
agents in JDM (38, 39). Bisphospho-
nates were prescribed to approximately
10% of patients seen in each decade.
Indications of these drugs in JDM in-
clude management of steroid-related
osteoporosis and calcinosis (40).

Our findings should be interpreted in
the light of some potential limitations.
All study data were recorded through
the retrospective review of clinical
charts. A retrospective analysis is sub-
ject to missing and possibly erroneous
data. We could not include information
regarding features of muscle biopsy,
nailfold capillary studies, magnetic
resonance imaging, or the presence of
myositis-specific autoantibodies or
HLA alleles.

In summary, we have described the
demographic features, disease charac-
teristics, diagnostic investigations, and
treatment modalities in the largest series
of children with JDM reported to date.
Our results highlight the current tenden-
cy toward early aggressive treatment,
namely with high-dose intravenous
methylprednisolone and methotrexate.
There were, however, several differ-
ences in the frequency of therapeutic
choices between European and Latin
American paediatric rheumatologists,
which reflect the scarcity of evidence-
based data on which to base treatment
decisions. This underscores the need of
developing uniform therapeutic proto-
cols for JDM, possibly based on the in-
vestigation of currently available ther-
apeutic regimens and novel medications
in randomised controlled trials.

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References
1. CASSIDY JT, LINDSLEY CB: Juvenile der-
matomyositis. In: CASSIDY JT, PETTY RE,
LAXER RM, LINDSLEY CB (Eds.): Textbook
of pediatric rheumatology. 5th ed. Philadel-
2. FELDMAN BM, RIDER LG, REED AM, PACH-
MAN LM: Juvenile dermatomyositis and
other idiopathic inflammatory myopathies
3. WEDDERBURN LR, LI CKC: Paediatric idi-
opathic inflammatory muscle disease. Best
4. HUBER A, FELDMAN BM: Long-term out-
comes in juvenile dermatomyositis: how did
we get here and where are we going? Curr
5. HUBER AM, LANG B, LEBLANC CM et al.: Med-
ium- and long-term functional outcomes in
a multicenter cohort of children with juve-
nile dermatomyositis. Arthritis Rheum 2000;
43: 541-9.
6. RIDER LG, LACHENBRUCH PA, MONROE JB
et al.: Damage extent and predictors in adult
and juvenile dermatomyositis and polymy-
ositis as determined with the myositis dam-
age index. Arthritis Rheum 2009; 60: 3425-
35.
7. RAVELLI A, TRAIL L, FERRARI C et al.: Long-
term outcome and prognostic factors of juve-
nile dermatomyositis: A multinational, mul-
ticenter study of 490 patients. Arthritis Care
8. RAMANAN AV, CAMPBELL-WEBSTER N, OTA
S et al.: The effectiveness of treating juvenile
dermatomyositis with methotrexate and ag-
gressively tapered corticosteroids. Arthritis
Rheum 2005; 52: 3570-78.
9. AL-MAYOUF SM, LAXER RM, SCHNEIDER R,
SILVERMAN ED, FELDMAN BM: Intravenous
immunoglobulin therapy for juvenile der-
matomyositis: efficacy and safety. J Rheu-
matol 2000; 27: 2496-503
10. HECKMATT J, HASSON N, SAUNDERS C et al.:
Cyclosporin in juvenile dermatomyositis.
11. COMPEYROT-LACASSAGNE S, FELDMAN
BM: Inflammatory myopathies in children.
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