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ORIGINAL ARTICLE

Long-Term Outcome and Prognostic Factors of Juvenile Dermatomyositis: A Multinational, Multicenter Study of 490 Patients

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Objective. **To investigate the long-term outcome and prognostic factors of juvenile dermatomyositis (DM) through a multinational, multicenter study.**

Methods. **Patients consisted of inception cohorts seen between 1980 and 2004 in 27 centers in Europe and Latin America. Predictor variables were sex, continent, ethnicity, onset year, onset age, onset type, onset manifestations, course type, disease duration, and active disease duration. Outcomes were muscle strength/endurance, continued disease activity, cumulative damage, muscle damage, cutaneous damage, calcinosis, lipodystrophy, physical function, and health-related quality of life (HRQOL).**

Results. **A total of 490 patients with a mean disease duration of 7.7 years were included. At the cross-sectional visit, 41.2–52.8% of patients, depending on the instrument used, had reduced muscle strength/endurance, but less than 10% had severe impairment. Persistently active disease was recorded in 41.2–60.5% of the patients, depending on the activity measure used. Sixty-nine percent of the patients had cumulative damage. The frequency of calcinosis and lipodystrophy was 23.6% and 9.7%, respectively. A total of 40.7% of the patients had decreased functional ability, but only 6.5% had major impairment. Only a small fraction had decreased HRQOL. A chronic course, either polycyclic or continuous, consistently predicted a poorer outcome. Mortality rate was 3.1%.**

Conclusion. **This study confirms the marked improvement in functional outcome of juvenile DM when compared with earlier literature. However, many patients had continued disease activity and cumulative damage at followup. A chronic course was the strongest predictor of poor prognosis. These findings highlight the need for treatment strategies that enable a better control of disease activity over time and the reduction of nonreversible damage.**

INTRODUCTION

Juvenile dermatomyositis (DM) is a multisystem disease of presumably autoimmune etiology that primarily involves the skin and muscles, but may affect many other organs (1). It is a rare illness, with an incidence of 2.5–4.1 cases per million children in the US (2) and 1.9 cases per million children in the UK (3), but accounts for a substantial proportion of patients seen in pediatric rheumatology clinics due to both its chronicity and potential severity.

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Prior to the early 1960s, there were no effective treatments for children with juvenile DM. As a result, outcomes for the disease were poor, with approximately one-third of the patients dying, one-third developing serious disability, and only one-third recovering without complications (4). In the early 1960s, after the introduction of corticosteroid therapy, the mortality rate dropped to less than 10% and there was a considerable improvement in functional outcome. Further refinement in the management of juvenile DM in the last 3 decades led to a further decrease in disease-related morbidity and in mortality, which is currently less than 2–3% (4). However, there are still many patients who are refractory or respond suboptimally to current treatments and experience continued disease activity. These patients are at risk of developing irreversible damage from the disease or its treatment. This damage may affect the quality of life of the patients and their family.

The dramatic reduction in the mortality of juvenile DM led to switching the attention in outcome studies from an initial interest primarily in survival to a greater focus on continued disease activity, muscle strength, physical function, cumulative organ damage, and health-related quality of life (HRQOL) (5). Furthermore, it has raised the need to search for prognostic factors that enable early identification of patients who are at greater risk of developing long-term morbidity. This is important because novel therapies that might be effective in the most severe and refractory forms are likely to become available shortly (6,7).

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There is little information on the long-term outcome of juvenile DM after the 1980s (4). Furthermore, studies are generally small and have used a variety of assessments, which hampers comparability of results. Most reports have focused on survival, disease activity, and calcinosis, and do not provide information on other important outcomes. Identification of prognostic factors has rarely been attempted. Against this background, we undertook a multinational, multicenter study whose primary aims were to investigate the long-term outcome of juvenile DM and to search for prognostic factors.

PATIENTS AND METHODS

Study design and patient selection. The study was the result of an international multicenter collaborative effort. To minimize a selection bias, investigators in each center were first asked to make a census of all of the patients seen between January 1980 and December 2004 and who had a diagnosis of juvenile DM by Bohan and Peter's criteria (8,9), were age <18 years at disease onset, and had at least 24 months of disease (i.e., followup) duration between disease onset and the time of the census. Patients were excluded if they initially had features suggestive of an overlap syndrome, such as scleroderma-like skin changes, or if they were lacking a rash (i.e., had juvenile polymyositis).

Next, each investigator was asked to retrieve the clinical charts of all of the patients who met the entry criteria, including those who had died. For each patient, investigators were instructed to collect retrospective data and to assess cumulative damage through the review of clinical data from disease onset to last followup visit or last visit before death. Investigators were also asked to make the cross-sectional assessment of all of the patients who were still followed or were no longer followed and were alive. Patients still followed could be assessed at a subsequent clinic visit, whereas patients lost to followup had to be contacted by telephone or mail and asked to go to the center to undergo the cross-sectional visit. 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 protocol was obtained in all of the participating countries. Outcome data were collected between 2003 and 2006.

Retrospective assessment. The following information was collected through the review of patient charts: sex; age at disease onset; ethnicity; date of disease onset and diagnosis (as recorded by the attending physician); date of onset of muscle and cutaneous disease (as derived from patient history); onset type (acute: with high fever, prostration, rash, and profound muscle weakness, or insidious: progressive development of muscle weakness and rash); presenting clinical features; severity of cutaneous and muscle disease at onset (from 1 = mild to 4 = very severe); course type, not including discontinuing 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) (10–12); cumulative duration of active disease (total number of months of disease activity); complications; death and its cause; and medications received during the disease course.

Damage assessment. Cumulative damage was assessed with the Myositis Damage Index (MDI) (13). Briefly, this tool assesses the extent of damage in the muscle, skeletal, cutaneous, gastrointestinal, pulmonary, cardiac, peripheral vascular, endocrine, ocular, infectious, malignancy, and other organs/systems. One portion of the instrument counts the items of damage developing in each organ/system. The other portion consists of a series of 10-cm visual analog scales (VAS) to quantify the severity of damage in the same organs/systems.

Cross-sectional assessment. The following clinical assessments were performed at the cross-sectional visit: muscle strength and function/endurance through the 8-muscle Manual Muscle Testing (MMT; normal = 80) by Kendall et al (14) and the Childhood Myositis Assessment Scale (CMAS; normal = 52) (15), respectively; overall disease activity through the Disease Activity Score (DAS) (16) and the Myositis Disease Activity Assessment VAS (MYOACT) (13); physical function through the Childhood Health Assessment Questionnaire (C-HAQ; 0 = normal, 3 = worst) (17,18); HRQOL through the parent version of the Child Health Questionnaire (CHQ), with calculation of the physical (PhS) and psychosocial (PsS) summary scores (these have been standardized to have a mean ± SD of 50 ± 10, with higher scores indicating better HRQOL) (18,19); and satisfaction with illness outcome (very satisfied, moderately satisfied, or not satisfied). The C-HAQ and the CHQ were also used in young adults to ensure harmonization with physical function and HRQOL data obtained in children and adolescents. Severe impairment in the MMT and the CMAS was defined as a score below the threshold that corresponds to a moderate level of C-HAQ disability (i.e., a score of 1.53), as previously found in children with juvenile idiopathic arthritis by Huber et al (20). Relationships between the MMT, the CMAS, and the C-HAQ were computed with linear regression models, and MMT and CMAS scores that corresponded to a moderate level of C-HAQ disability were calculated. These values were assumed to be an estimate of the median MMT and CMAS scores that would be seen at a moderate level of physical disability. Due to the relative aversion to extremes that is often seen when using VAS, with very low values (0.1 or 0.2 cm) being frequently obtained when the assessor actually intended to mark the end of the line, all VAS were considered abnormal when >0.2. Determination of serum muscle enzymes (creatine kinase, lactate dehydrogenase [LDH], aldolase, aspartate aminotransferase, and alanine aminotransferase) was optional and was performed only if deemed clinically indicated by the local investigator.

Training of study investigators. A training session on study design and assessments for the members of the Italian Pediatric Rheumatology Study Group was held in Genoa, Italy, on March 7–8, 2003. Training sessions on juvenile DM outcome measures were organized by the Paediatric Rheumatology International Trials Organisation (PRINTO) during the 2001 meeting of the Pediatric Rheumatology European Society in Utrecht, The Netherlands, and during a consensus conference held in 2001 in Pavia, Italy (21). Four fellows trained at the coordinating center (LT, FR, ES, EF) spent 3 months in the centers in Latin America and in the UK and assisted the local investigators in making study assessments.

Statistical analysis. 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 by means of the chi-square or Fisher's exact test, as appropriate, in case of categorical data. The separate (univariate) and joint (multivariate) effects of predictor variables on long-term outcomes were examined. Predictor variables were sex, continent, ethnicity, 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 HRQOL. Bivariate analyses were first made for each outcome. Then, multiple logistic regression analyses were carried out by entering predictor variables as explanatory variables and each disease outcome as an outcome variable. Cases with missing data were excluded. Before performing univariate and multivariate analyses, continuous predictor variables were converted to binary variables using the cut points obtained through the receiver operating characteristic (ROC) curve analysis. 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 odd ratios and 95% confidence intervals were calculated; statistical significance was tested by means of the likelihood ratio test. The area under the ROC curve of the best-fitting model and the Count R^2 were used as indicators of the predictive ability of the model.

All statistical tests were 2-sided; *P* values less than 0.05 were considered statistically significant. The statistical packages used were Statistica (StatSoft, Tulsa, OK) and Stata, release 7 (StataCorp, College Station, TX).

RESULTS

A total of 606 patients were included in the census by 27 pediatric rheumatology centers in 5 countries (Argentina, Brazil, Italy, Mexico, and the UK). 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 followup duration of <2 years or undetermined. The remaining 490 patients were included in the study. All of these patients received the retrospective assessment, 462 (94.3%) had the cumulative damage assessed, and 392 (80%) underwent

Table 1. Assessment of muscle strength/endurance, overall disease activity, and muscle enzymes at the cross-sectional visit*

	All patients (n = 392)		Europe (n = 216)		Latin America (n = 176)		
	N	No. (%)	N	No. (%)	N	No. (%)	P†
Patients with total MMT score <80	347	143 (41.2)	208	81 (38.9)	139	62 (44.6)	0.29
Patients with total MMT score <64‡	347	24 (6.9)	208	13 (6.2)	139	11 (7.9)	0.55
Patients with MMT score <10 in each muscle group							
Neck flexors	347	100 (28.9)	208	57 (27.4)	139	44 (31.7)	0.39
Shoulder abductors	347	68 (19.6)	208	41 (19.7)	139	27 (19.4)	0.95
Elbow flexors	347	49 (14.1)	208	29 (13.9)	139	20 (14.4)	0.91
Wrist extensors	347	44 (12.7)	208	29 (13.9)	139	15 (10.8)	0.39
Hip extensors	347	96 (27.7)	208	49 (23.6)	139	47 (33.8)	0.036
Hip abductors	347	79 (22.8)	208	43 (20.7)	139	36 (25.9)	0.26
Knee extensors	347	56 (16.1)	208	37 (17.8)	139	19 (13.7)	0.31
Ankle dorsiflexors	347	38 (11.0)	208	20 (9.6)	139	18 (12.9)	0.33
Patients with CMAS score <52	373	197 (52.8)	203	90 (44.3)	170	107 (62.9)	0.0003
Patients with CMAS score <35‡	373	31 (8.3)	203	12 (5.9)	170	19 (11.2)	0.07
Patients with DAS >0	352	213 (60.5)	213	138 (64.8)	139	75 (54.0)	0.042
Patients with MYOACT global disease activity VAS >0.2	313	129 (41.2)	188	90 (47.9)	125	39 (31.2)	0.003
Patients with VAS >0.2 in each MYOACT domain							
Constitutional	328	51 (15.5)	190	30 (15.8)	138	21 (15.2)	0.89
Cutaneous	331	124 (37.5)	191	84 (44.0)	140	40 (28.6)	0.004
Skeletal	329	36 (10.9)	190	22 (11.6)	139	14 (10.1)	0.67
Gastrointestinal	327	8 (2.4)	190	3 (1.6)	137	5 (3.6)	0.29§
Pulmonary	325	16 (4.9)	189	8 (4.2)	136	8 (5.9)	0.50
Cardiovascular	323	2 (0.6)	189	0 (0.0)	134	2 (1.5)	0.17§
Muscle	326	86 (26.4)	189	53 (28.0)	137	33 (24.1)	0.42
Patients with abnormal serum muscle enzymes							
Any enzyme	174	69 (39.7)	78	24 (30.8)	96	45 (46.9)	0.031
Creatine kinase	154	35 (22.7)	70	12 (17.1)	84	23 (27.4)	0.13
Lactic dehydrogenase	146	42 (28.8)	67	13 (19.4)	79	29 (36.7)	0.021
Aspartate aminotransferase	154	13 (8.4)	67	4 (6.0)	87	9 (10.3)	0.33
Alanine aminotransferase	154	19 (12.3)	69	7 (10.1)	85	12 (14.1)	0.46

* MMT = Manual Muscle Testing; CMAS = Childhood Myositis Assessment Scale; DAS = Disease Activity Score; MYOACT = Myositis Disease Activity Assessment VAS of the Myositis Disease Activity Assessment Tool; VAS = visual analog scale.
† Europe versus Latin America. *P* values refer to the chi-square test unless otherwise specified.
‡ Severe impairment (see Patients and Methods for definition).
§ Fisher's exact test.

the cross-sectional visit. The 98 patients (20%) who did not undergo the cross-sectional assessment had died (n = 15 [3.1%]), could not be located, or declined to go to the center for the visit.

Of the 490 study patients, 248 (50.6%) were enrolled in Europe (168 in Italy and 80 in the UK) and 242 (49.4%) were enrolled in Latin America (117 in Brazil, 75 in Argentina, and 50 in Mexico). A total of 321 patients (65.5%) were girls and 320 (65.3%) were white. The mean age at disease onset was 6.9 years (range 0.9–17.8 years) and the mean disease duration at the cross-sectional visit was 7.7 years (range 2–25.2 years). The onset type was acute in 271 patients (57%) and insidious in 204 patients (43%). The course type was monocyclic in 198 patients (41.3%) and chronic polycyclic or continuous in 281 patients (58.7%). The most common clinical manifestations at disease onset were muscle weakness (84.9%), Gottron's papules (72.9%), heliotrope rash (62%), malar rash (56.7%), and arthritis (35.7%). The main clinical features, including demographic characteristics, of European and Latin American patients were comparable. In particular, the mean ± SD age at disease onset and the mean disease duration were 6.9 ± 3.7 years and 8 ± 5.2 years, respectively, in European patients and 6.9 ± 4.1 years and 7.4 ± 4.6 years, respectively, in Latin American patients. The frequency of acute and insidious onset was 60.7% and 39.3%, respectively, in European patients and 53.2% and 46.8%, respectively, in Latin American patients. The frequency of monocyclic and chronic polycyclic/continuous course was 39.3% and 60.7%, respectively, in European patients and 43.5% and 56.5%, respectively, in Latin American patients. Overall, the characteristics of the study patients were similar to those of recently described juvenile DM cohorts (12,22,23).

Table 1 shows the results of the assessment of muscle strength, disease activity, and muscle enzymes at the cross-sectional visit. Evidence of muscle weakness was detected in 41.2% and 52.8% of the patients who had

Table 2. Frequency of cumulative damage (visual analog scale >0.2) by organ/system

	All patients (n = 462)		Europe (n = 245)		Latin American (n = 217)		
	N	No. (%)	N	No. (%)	N	No. (%)	*P**
Cutaneous	449	238 (53.0)	238	132 (55.5)	211	106 (50.2)	0.27
Muscle	449	154 (34.3)	239	71 (29.7)	210	83 (39.5)	0.029
Skeletal	451	125 (27.7)	239	69 (28.9)	212	56 (26.4)	0.56
Endocrine	445	82 (18.4)	237	28 (11.8)	208	54 (26.0)	0.0001
Gastrointestinal	448	38 (8.5)	238	14 (5.9)	210	24 (11.4)	0.036
Pulmonary	443	26 (5.9)	234	9 (3.8)	209	17 (8.1)	0.06
Infection	449	27 (6)	238	12 (5.0)	211	15 (7.1)	0.36
Ocular	449	11 (2.4)	238	5 (2.1)	211	6 (2.8)	0.61
Cardiovascular	445	13 (2.9)	237	9 (3.8)	208	4 (1.9)	0.24
Peripheral vascular	448	7 (1.6)	237	7 (3.0)	211	0 (0)	0.016†
Malignancy	447	0 (0)	236	0 (0)	211	0 (0)	–
Any organ/system	455	314 (69.0)	240	159 (66.2)	215	155 (72.1)	0.18
Global damage	399	252 (63.2)	230	146 (63.5)	169	106 (62.7)	0.88

* Europe versus Latin America. *P* values refer to the chi-square test unless otherwise specified.
† Fisher's exact test.

abnormal MMT and CMAS scores, respectively. However, only 6.9% and 8.3% of the patients had severe impairment in MMT and CMAS scores, respectively. Persistently active disease, as shown by a DAS score >0 and a MYOACT global disease activity VAS >0.2, was recorded in 60.5% and 41.2% of the patients, respectively. Ongoing disease activity was seen most frequently in the cutaneous, muscle, constitutional, and skeletal domains on the MYOACT. The mean ± SD MMT, CMAS, and DAS scores were 76.1 ± 9.1, 46.9 ± 9.9, and 2.9 ± 3.6, respectively. Elevation of at least one muscle enzyme was seen in 39.7% of the patients, with the most and least frequently elevated enzymes being the LDH and the aspartate aminotransferase, respectively.

Sixty-nine patients had damage in one or more organ systems, with the skin being the most frequently affected, followed by muscle, skeletal, and endocrine organ systems (Table 2). Cutaneous scarring/atrophy was the most common damage item, followed by muscle atrophy, calcinosis, and joint contractures (Table 3).

The results obtained for functional ability, pain, HRQOL, and parental satisfaction with illness outcome are shown in Table 4. At the cross-sectional assessment, 40.7% of the patients had decreased functional ability, as shown by a C-HAQ score >0. However, only 6.5% of the patients had severe functional impairment (C-HAQ score >1.5). The most impaired C-HAQ categories were reach, dressing, and activities hygiene, whereas walking was the least impaired. Approximately 35% of the patients had pain. Decreased HRQOL in the physical and psychosocial domains was noted in 10.5% and 12.8% of the patients, respectively, with less than 5% of the patients showing major impairment. The mean ± SD C-HAQ, CHQ PhS, and CHQ PsS scores were 0.34 ± 0.64, 51.0 ± 7.8, and 49.7 ±

Table 3. Frequency of specific damage items

	All patients (n = 462)		Europe (n = 245)		Latin America (n = 217)		
	N	No. (%)	N	No. (%)	N	No. (%)	*P**
Cutaneous scarring/atrophy	443	195 (44)	232	115 (49.6)	211	80 (37.9)	0.014
Muscle atrophy	448	106 (23.7)	233	60 (25.8)	215	46 (21.4)	0.28
Calcinosis	450	106 (23.6)	235	50 (21.3)	215	56 (26.0)	0.23
Joint contractures	448	82 (18.3)	233	43 (18.5)	215	39 (18.1)	0.93
Muscle dysfunction	441	72 (16.3)	229	16 (7.0)	212	56 (26.4)	< 0.0001
Muscle weakness	446	48 (10.8)	232	22 (9.5)	214	26 (12.1)	0.36
Lipodystrophy	444	43 (9.7)	233	20 (8.6)	211	23 (10.9)	0.41
Hirsutism	431	44 (10.2)	222	11 (5.0)	209	33 (15.8)	0.0002
Growth failure	424	34 (8)	219	14 (6.4)	205	20 (9.8)	0.20
Osteoporosis with fractures	435	26 (6)	233	14 (6.0)	202	12 (5.9)	0.98
Dysphagia	442	24 (5.4)	232	6 (2.6)	210	18 (8.6)	0.006
Cataract	430	9 (2.1)	225	3 (1.3)	205	6 (2.9)	0.32†
Gastrointestinal infarction/resection	444	7 (1.6)	232	4 (1.7)	212	3 (1.4)	1.00†

* Europe versus Latin America. *P* values refer to the chi-square test unless otherwise specified.
† Fisher's exact test.

Table 4. Assessment of functional ability, well-being, pain, health-related quality of life, and satisfaction about the outcome of the illness at the cross-sectional assessment*

	All patients (n = 392)		Europe (n = 216)		Latin America (n = 176)		
	N	No. (%)	N	No. (%)	N	No. (%)	P†
Patients with C-HAQ score >0	339	138 (40.7)	196	74 (37.8)	143	64 (44.8)	0.20
Patients with C-HAQ score 0	339	201 (59.3)	196	122 (62.2)	143	79 (55.2)	0.60
Patients with C-HAQ score >0 and ≤0.5	339	69 (20.3)	196	38 (19.4)	143	31 (21.7)	0.60
Patients with C-HAQ score >0.5 and ≤1.5	339	47 (13.9)	196	25 (12.8)	143	22 (15.4)	0.49
Patients with C-HAQ score >1.5	339	22 (6.5)	196	11 (5.6)	143	11 (7.7)	0.44
Patients with score >0 in each C-HAQ category							
Dressing	339	75 (22.1)	194	47 (24.2)	145	28 (19.3)	0.28
Arising	339	60 (17.7)	194	29 (14.9)	145	31 (21.4)	0.12
Eating	339	60 (17.7)	194	34 (17.5)	145	26 (17.9)	0.92
Walking	339	45 (13.3)	194	27 (13.9)	145	18 (12.4)	0.69
Hygiene	339	65 (19.2)	194	36 (18.6)	145	29 (20.0)	0.74
Reach	339	90 (26.5)	194	43 (22.2)	145	47 (32.4)	0.034
Grip	339	65 (19.2)	194	31 (16.0)	145	34 (23.4)	0.08
Activities	339	76 (22.4)	194	45 (23.2)	145	31 (21.4)	0.69
Patients with pain VAS >0.2	339	119 (35.1)	194	76 (39.2)	145	43 (29.7)	0.07
Patients with CHQ PhS score <40 (1 SD below the mean of healthy controls)	287	26 (9.1)	165	18 (10.9)	122	8 (6.6)	0.20
Patients with CHQ PhS score <30 (2 SDs below the mean of healthy controls)	287	11 (3.8)	165	8 (4.8)	122	3 (2.5)	0.36‡
Patients with CHQ PsS score <40 (1 SD below the mean of healthy controls)	287	40 (13.9)	165	20 (12.1)	122	20 (16.3)	0.30
Patients with CHQ PsS score <30 (2 SDs below the mean of healthy controls)	287	9 (3.1)	165	2 (1.2)	122	7 (5.7)	0.04‡
Satisfaction about the outcome of the illness	187		102		85		1.00
Very satisfied		128 (68.4)		70 (68.6)		58 (68.2)	
Moderately satisfied		48 (25.7)		26 (25.5)		22 (25.9)	
Not satisfied		11 (5.9)		6 (5.9)		5 (5.9)	

* C-HAQ = Childhood Health Assessment Questionnaire; VAS = visual analog scale; CHQ = Child Health Questionnaire; PhS = physical summary score; PsS = psychosocial summary score.
† Europe versus Latin America. *P* values refer to the chi-square test unless otherwise specified.
‡ Fisher's exact test.

8.7, respectively. A total of 68% of the parents/patients reported being very satisfied with the outcome of the illness; 25% were moderately satisfied and only 5.9% were not satisfied.

Table 5 shows the best-fitting models of logistic regression analyses obtained for the prediction of muscle weakness or continued disease activity at the cross-sectional assessment. Latin American patients were more likely to have an impaired CMAS, but were less likely to have persistently active disease. An insidious disease onset predicted continued disease activity on both the DAS and the MYOACT, whereas a longer duration of followup was associated with a lesser likelihood of MMT impairment and continued disease activity on the MYOACT. A chronic course, either polycyclic or continuous, was consistently predictive for all of the outcomes.

The logistic regression models for damage, calcinosis, and lipodystrophy are shown in Table 6. Latin American patients were more likely than European patients to have muscle damage, calcinosis, and lipodystrophy. A chronic course, either polycyclic or continuous, predicted all of the outcomes except lipodystrophy. A longer followup duration predicted global and muscle damage. Both calcinosis and lipodystrophy were associated with a greater cumulative duration of active disease.

Logistic regression analyses obtained for physical function and HRQOL showed that female patients had a greater likelihood of being functionally impaired at the cross-sectional visit. A chronic course, either polycyclic or continuous, was predictive of deterioration in physical function and physical HRQOL. Surprisingly, a longer duration of active disease had a protective effect toward impairment in psychosocial HRQOL (data not shown).

DISCUSSION

We investigated the long-term outcome and prognostic factors of juvenile DM in a large series of patients who were inception cohorts seen in 27 centers in 5 countries in 2 continents. Owing to its size and sampling method, the study population is likely representative of patients with this disease seen in most tertiary pediatric rheumatology centers and covers the entire spectrum of disease phenotype and severity. A bias toward the inclusion of patients still followed at the study centers who were more likely to have persistently active disease and accumulated damage

Table 5. Best-fitting model for predictors of muscle strength and continued active disease obtained through logistic regression procedures*

Predictors	MMT score <80 (n = 133/332 [40.1%]), OR (95% CI)	CMAS score <52 (n = 182/350 [52.0%]), OR (95% CI)	DAS >0 (n = 196/324 [60.5%]), OR (95% CI)	MYOACT global disease activity VAS >0 (n = 119/278 [42.8%]), OR (95% CI)
Sex (female/male)	1.75 (1.06–2.91)†	1.88 (1.15–3.06)†		
Continent (Latin America/ Europe)		3.05 (1.88–4.95)‡	0.55 (0.33–0.92)†	0.37 (0.20–0.66)‡
Onset year				
1991–2000/1980–1990		2.81 (1.23–6.39)†		
2001–2004/1980–1990		3.40 (1.39–8.29)		
Onset age, years				
>5–9.9/≥10		1.01 (0.55–1.87)†		
≤5/≥10		1.97 (1.03–3.77)		
Onset type (insidious/acute)			1.89 (1.15–3.12)†	3.37 (1.72–6.60)‡
Cutaneous manifestations at onset (yes/no)		0.31 (0.10–0.91)†		4.98 (1.31–18.84)†
Dysphagy/dysphonia at onset (yes/no)		2.11 (1.17–3.78)†		
Severity of muscular manifestations at onset				
Moderate/mild				3.18 (1.54–6.56)§
Severe/mild				3.10 (1.31–7.34)
Course type (chronic polycyclic or continuous/monocyclic)	2.91 (1.77–4.78)‡	2.42 (1.49–3.91)‡	5.15 (3.14–8.46)‡	5.48 (2.94–10.20)‡
Followup duration, years				
5–9.9/2–4.9	0.70 (0.41–1.19)‡			0.56 (0.30–1.05)‡
≥10/2–4.9	0.27 (0.15–0.51)			0.24 (0.12–0.49)
Area under the ROC curve of the model	0.70	0.73	0.73	0.78
Count R^2	0.65	0.64	0.71	0.70

* *P* values refer to the likelihood ratio test. MMT = Manual Muscle Testing; OR = odds ratio; 95% CI = 95% confidence interval; CMAS = Childhood Myositis Assessment Scale; DAS = Disease Activity Score; MYOACT = Myositis Disease Activity Assessment VAS of the Myositis Disease Activity Assessment Tool; VAS = visual analog scale; ROC = receiver operating characteristic.
† $P < 0.05$.
‡ $P < 0.001$.
§ $P < 0.01$.

is unlikely, because 94.3% of the 490 patients who met the eligibility criteria had cumulative damage assessed and 80% underwent the cross-sectional visit. Importantly, the disease status at the cross-sectional visit was evaluated by both patient/parent-centered and physician-centered measures, with the physician being requested to assess the disease outcomes in each patient through a detailed clinical evaluation.

At the cross-sectional assessment, after an average of 7.7 years of disease duration, approximately 40% of the patients had reduced muscle strength, as measured with the MMT, and approximately half of the patients had impaired muscle function/endurance, as assessed with the CMAS. However, only 6.9% and 8.3% of the patients had severe weakness, defined as an MMT or CMAS score corresponding to a moderate level of C-HAQ disability (20), respectively, suggesting that muscle impairment was mild in most cases. Latin American patients, who had a greater frequency of muscle damage than did European patients, also had a greater frequency of CMAS impairment, whereas the proportion of patients with abnormal MMT was comparable in the two cohorts. This suggests that assessment of muscle function/endurance with the CMAS may help distinguish muscle damage from muscle activity better than measurement of peak muscle force with the MMT. Likewise, the "muscle dysfunction" item of the MDI was significantly more common in Latin American patients than in European patients, whereas the "muscle weakness" item was equally represented in the two continental populations.

A sizable proportion of the patients had persistently active disease at the cross-sectional visit, as shown by the 60.5% or 41.2% frequency of abnormal DAS or MYOACT global disease activity scale, respectively. As expected, disease activity was seen much more frequently in the skin and (to a lesser extent) in the skeletal muscles, which are the organ/system most commonly affected in juvenile DM. Increased levels of muscle enzymes were seen in 39.7% of the patients, with the LDH being the most frequently abnormal. A similarly high frequency of persistently active disease at the time of followup was reported in a Canadian multicenter study by Huber et al (5), who found that 40% of the patients continued to have a rash and 23% reported weakness.

Cumulative damage as assessed with the MDI was common, with 69% of the patients having at least one damage

Table 6. Best-fitting model for predictors of the presence of cumulative damage in at least one organ/system, muscle damage, cutaneous damage, calcinosis, and lipodystrophy obtained through logistic regression procedures*

	Cumulative damage (n = 273/366 [74.6%]), OR (95% CI)	Muscle damage (n = 137/366 [37.4%]), OR (95% CI)	Cutaneous damage (n = 201/356 [56.5%]), OR (95% CI)	Calcinosis (n = 94/360 [26.1%]), OR (95% CI)	Lipodystrophy (n = 37/354 [10.4%]), OR (95% CI)
Continent (Latin American/Europe)		2.36 (1.49–3.75)†		3.05 (1.69–5.51)†	2.34 (1.11–4.93)‡
Onset year					
1991–2000/1980–1990				0.48 (0.22–1.04)‡	
2001–2004/1980–1990				0.26 (0.10–0.65)	
Age at onset, years					
≥5–9.9/<5				1.58 (0.68–3.67)‡	
≥10/<5				2.91 (1.23–6.91)	
Muscle weakness at onset (yes/no)		2.45 (1.22–4.94)§			
Severity of cutaneous manifestations at onset					
Moderate/mild			1.36 (0.81–2.29)§		
Severe/mild			3.21 (1.49–6.95)		
Course type (chronic polycyclic or continuous/monocyclic)	5.17 (3.07–8.69)†	3.57 (2.18–5.86)†	3.71 (2.20–6.26)†	2.60 (1.31–5.17)§	
Active disease duration, months					
13–24/0–12			1.37 (0.74–2.54)§	3.64 (1.37–9.62)†	
≥25/0–12			2.57 (1.39–4.76)	7.91 (3.14–19.95)	15.57 (5.20–46.63)¶
Followup duration, years					
5–9.9/2–4.9	2.43 (1.28–4.60)§	1.93 (1.14–3.28)‡			
≥10/2–4.9	0.92 (0.51–1.68)	0.94 (0.53–1.69)			
Area under the ROC curve of the model	0.73	0.70	0.76	0.80	0.78
Count R^2	0.74	0.66	0.69	0.77	0.89

* *P* values refer to the likelihood ratio test. OR = odds ratio; 95% CI = 95% confidence interval; ROC = receiver operating characteristic.
† $P < 0.001$.
‡ $P < 0.05$.
§ $P < 0.01$.
¶ Duration of active disease (≥25 months/0–24 months). $P < 0.001$.

item and 63.2% being scored as >0.2 on the global damage VAS. As for disease activity, the skin and, to a lesser extent, the skeletal muscles were the organs/systems most frequently affected. Skeletal damage was third in order of frequency, mostly due to joint contractures. Endocrine damage, primarily related to growth failure, was recorded in 19.3% of the patients. The gastrointestinal was the most frequently involved visceral organ/system, with dysphagia being most common. Overall, these findings show that the percentage of patients with juvenile DM who develop damage is substantial and needs to be improved.

Impairment in physical function, defined as a C-HAQ score >0, was demonstrated in 40.7% of the patients. However, only 6.5% of the patients had serious functional disability (i.e., a C-HAQ score >1.5). A similar frequency of favorable functional outcome was reported by Huber et al (5). The most and least impaired activities were "reach" and "walking," respectively. This suggests that the negative effect of muscle weakness on the activities of daily living in patients with juvenile DM is largely related to the involvement of the upper girdle muscles, whereas the impact on the ability to walk is limited. The results provided by HRQOL assessment were quite reassuring, with only a few patients showing major impairment in their physical or psychosocial well-being. In contrast to the predominant involvement of physical health found in other pediatric rheumatic diseases (24,25), the physical and psychosocial domains were equally affected. Parallel to HRQOL findings, 68.4% of the parents/patients declared themselves as being very satisfied with the outcome of the illness and only 5.9% reported not being satisfied. The frequency of satisfaction/dissatisfaction observed in our study is very similar to that reported by Huber et al (5).

A rational approach to the management of juvenile DM is hampered by the paucity of information on predictors of disease outcome. Several studies have shown that delay in treatment or the administration of low-dose treatment predicts poor functional outcome and the development of calcinosis (11,26,27). Recently, the presence of a rash at 3 months after diagnosis and of nailfold abnormalities and a rash at 6 months have been found to predict a longer time to remission (12). The most relevant finding of our analysis of outcome predictors was that the chronic course, either polycyclic or persistent, consistently predicted a poorer outlook for most of the outcomes investigated, including functional ability and HRQOL in the physical domain. Furthermore, calcinosis and lipodystrophy, which are important disease complications, were associated with a greater cumulative duration of active disease. As found by Huber et al (5), female patients had a greater likelihood of developing long-term functional impairment. The apparently paradoxical observation that a longer duration of active disease was protective toward impairment in psychosocial HRQOL suggests that patients' social, mental, and emotional health may adapt and improve over time.

Some potential caveats should be taken into account in interpreting our findings. Predictor variables were assessed through the retrospective review of clinical charts. A retrospective analysis is subject to missing and possibly erroneous data. During the wide timeframe of patient inclusion (1980–2004), the treatment approach to juvenile DM has varied considerably, with patients seen in the earlier years being more likely to have received corticosteroids alone and those treated in the recent years being more likely to have received adjunctive therapy with immunosuppressive medications or intravenous immunoglobulin. However, the relative effect of different treatment regimens on disease outcome could not be evaluated. A formal definition of inactive disease or clinical remission in the evaluation of disease outcome was not used in outcome assessment. Not all patients underwent formal evaluation for some damage items, such as osteoporosis. Finally, we did not attempt to correlate features of muscle biopsy, nailfold capillary studies, magnetic resonance imaging, or the presence of myositis-specific autoantibodies or HLA alleles with disease outcomes.

In conclusion, our patients with juvenile DM had favorable functional outcomes, with only a few of them showing severe muscle weakness or physical disability at the followup assessment. Furthermore, most patients had good HRQOL and were satisfied with the outcome of the illness. The mortality rate was 3.1%. These findings are in keeping with those obtained in recent surveys (5) and confirm the marked improvement in disease prognosis when compared with the literature of the 1960s and 1970s (4). However, many patients continued to have chronic disease activity and had evidence of cumulative damage. A chronic course of the illness was the most consistent predictor of a poorer long-term outcome in terms of muscle weakness, continued disease activity, cumulative damage, and functional impairment. Development of calcinosis and lipodystrophy was associated with greater duration of active disease. These findings highlight the critical need for treatments and treatment strategies that have the ability to better control disease activity over time and to reduce the development of nonreversible organ damage.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ravelli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Ravelli, Pistorio.

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