Disease course, frequency of relapses and survival of 73 patients with juvenile or adult dermatomyositis

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Abstract

Objective

Our aim is to present the disease course, frequency of relapses and survival of juvenile and adult dermatomyositis (JDM/DM) patients.

Methods

Analysis was performed using data on 73 patients. The median follow-up for 38 JDM patients was 32 months and 78 months for 35 adult DM patients.

Results

23/38 JDM patients (60%) had monophasic, 12/38 (31.6%) had polycyclic and 3/38 (7.9%) had chronic disease. Among children treated only with glucocorticoids, 12/20 (60%) had monophasic and 8/20 (40%) had polycyclic disease. 10/17 (58.8%) children, who required second-line immunosuppressive agents, had monophasic and 4/17 (23.5%) had polycyclic disease. 18/35 DM (51.4%) patients had monophasic, 13/35 (37.1%) had polycyclic, 1/35 (2.9%) had chronic disease and 3/35 (8.6%) had fulminant myositis. Among DM patients requiring only glucocorticoids, 12/20 (60%) were monophasic and 8/20 (40%) were polycyclic. In patients requiring second-line immunosuppressive agents, 6/15 patients (40%) had monophasic and 5/15 (33.3%) had polycyclic disease. Among patients with polycyclic disease, the risk of relapse was higher during first year than later in the disease course. None of the JDM patients have died, while 4 disease-specific deaths occurred in adult patients. There was no significant difference between the survival of JDM and DM patients.

Discussion

There was no correlation between relapse-free survival and the initial therapeutic regimen. Many of our patients had polycyclic or chronic disease. As relapses can occur after a prolonged disease-free interval, patients should be followed for at least 2 years. Although we found a favourable survival rate, further investigations are needed to assess functional outcome.

Key words

Juvenile and adult dermatomyositis, disease course, relapse risk, survival analysis.

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Abbreviation used in this article:

AZA:	azathioprine
CAM:	cancer-associated myositis
CK:	creatinine-kinase
CYA:	cyclosporine A
CYC:	cyclophosphamide
CI:	confidence interval
DM:	dermatomyositis
HRCT:	high-resolution computerized tomography
IIM:	idiopathic inflammatory myopathy
ILD:	interstitial lung disease
IVIG:	intravenous immunoglobuline
JDM:	juvenile dermatomyositis
LDH:	lactate-acid dehydrogenase
MTX:	methotrexate
OM:	overlap myositis
PM:	polymyositis

Introduction

The idiopathic inflammatory myopathies (IIMs) are systemic autoimmune diseases characterized by chronic muscle inflammation resulting in progressive weakness and cutaneous lesions (heliotrope rash, Gottron's papules, Gottron's sign and V-sign) in the case of dermatomyositis. The frequent extraskeletal- and extramuscular manifestations, mainly the involvement of the pulmonary, gastrointestinal and cardiac systems, considerably contributes to the morbidity and mortality of the disease.

IIMs affect both children and adults. In childhood, the most frequent subgroup is juvenile dermatomyositis (JDM). The first case of JDM was reported by Potain (14). Children with JDM have a better prognosis than adult DM patients. The association of cancer with JDM is rare (6, 16). For the most frequent myopathies, polymyositis (PM) and DM, mortality was 50% within one year before the widespread use of glucocorticoids (1). In the past decades, earlier diagnosis and more aggressive immunosuppressive treatment regimens have become the standard of care, so the survival of patients with IIMs has progressively improved worldwide (7, 18).

The goal of medical therapy is to prevent acute muscular damage, chronic muscular atrophy and contracture, to prevent disease relapses, and last but not least to restore at least in part the patient's quality of life (1,13). Treatment of JDM/DM is based on immune suppression with first-line agent glucocorticoids starting with a dose of 1-2 mg/kg/day of prednisolone or an equivalent. This traditional therapy is effective in about 60-80% of patients with juvenile or adult DM (1,8, 11). Glucocorticoids are considered to be ineffective if after 3 months the muscular weakness does not abate or the disease flares again after a dose reduction (1). In these cases or when severe side effects occur, additional immunosuppressants such as azathioprine (AZA), methotrexate (MTX), cyclosporine A (CYA), intravenous immunoglobulin (IVIG) and cyclophosphamide (CYC) (second-line agents) can be used (10, 15, 16, 20). Up to 20-40% of myositis patients require not only glucocorticoids, but other immunosuppressive therapy as well. Recently many authors have promoted the use of second-line drugs early in the course of the illness along with glucocorticoids (2,4,19), especially when the prognosis is considered to be poor (Table I).

We report here the first study of 38 Hungarian JDM patients, in whom the disease course, frequency of relapses and survival were investigated. We examined the relationship between the type of initial treatment and the subsequent clinical course. Furthermore, we compared our data on JDM patients with data on adult primary, idiopathic DM patients. To our best knowledge, this constitutes one of the largest studies comparing the clinical course and survival of juvenile and adult DM patients published to date.

Methods

Patient selection

In this study, 38 consecutive juvenile in- and out-patients were identified who had been diagnosed, treated and followed-up by the 2ndDepartment of

Table I. Classical factors for a poor prognosis in juvenile and adult DM (refs. 5, 6, 7, 9).

- Acute, severe disease led to life threatening situation
- Severe dysphagia led to possible risk of aspiration
- Cardiac involvement
- Dysphonia
- Interstitial lung disease
- Vasculitis
- Positive anti-synthetase (anti-Jo-1) or anti-SRPautoantibody test
- Delay of diagnosis and treatment
- Inadequate treatment
- Older age
- Male sex
- African-American race
- Associated malignancy

Pediatrics, Semmelweis University, Faculty of Medicine; the 3rd Department of Internal Medicine, University of Debrecen; the National Institute of Rheumatology and Physiotherapy and Heim Pál Children's Hospital. We compared data on these JDM patients with data on 35 adult primary, idiopathic DM patients, who had been diagnosed, treated and followed-up by the 3rd Department of Internal Medicine, University of Debrecen. The diagnosis of DM was made between January 1, 1976 and December 31, 2002.

We analyzed the medical records retrospectively, recording the following data: age, sex, the time of diagnosis; the type of clinical course and the date of death or the end of follow-up; the initial treatment and the treatment which led to remission; and extraskeletal and extramuscular manifestations at any time during the clinical course. We decided not to analyze the parameter of myositis-specific autoantibodies because this assay was not carried out in all of the patients in the study. All patients were Caucasian. There were no missing values among the investigated factors in the dataset. Patients with juvenile or adult PM, with overlap myositis or cancer-associated myositis (CAM) were excluded.

Diagnosis

In all cases the diagnosis of DM was based upon the criteria defined by Bohan and Peter (3):

1. Progressive, symmetrical weakness of the proximal muscles;
2. Raised creatinine-kinase (CK) and lactate-acid dehydrogenase (LDH) enzyme activity in the serum;
3. Characteristic triad of electromyographic alterations;
4. Muscle biopsy evidence;
5. Characteristic dermatologic features.

Confidence limits were defined as follows: definite (consisting of 3 or 4 criteria, plus rash), probable (comprising 2 criteria and rash), and possible (including 1 criterion and rash) (3).

Thirty-one patients had definite and 7 patients had probable JDM. All of the adult patients had definite disease. Patients with a possible diagnosis were excluded.

Definition of extramuscular and extraskeletal manifestations:

At the time of diagnosis, all patients underwent a clinical evaluation to detect extramuscular and extraskeletal manifestations. ECG, chest radiograph and pulmonary function tests were performed in each case. HRCT and echocardiography were carried out if alarming signs and symptoms were detected during the physical examination or during previous screening tests. Later on in the clinical course of the disease, these tests were usually repeated annually or as required (e.g. if a relapse occurred).

Interstitial lung disease (ILD) was considered to be present if chest radiograph and/or high-resolution computed tomography (HRCT) scan indicated bibasilar interstitial fibrosis or alveolar infiltrates and pulmonary function tests showed abnormalities characterized by a restrictive pattern.

Diagnosis of cardiac involvement was based upon the exclusion of other causes of rhythm disturbances, conduction defects, myocarditis, cardiomyopathy and congestive heart failure.

Respiratory muscle involvement is a result of weakness of the respiratory musculature in DM and it was considered to be present if patients exhibited ventilatory failure with decreased vital capacity.

Disease course

Patients were classified into 4 groups based on their disease course: (i) fulminant onset disease, (ii) monophasic, (iii) polycyclic and (iv) chronic. In fulminant onset disease, life-threatening events occurred which led to death. The disease course was considered to be monophasic if a single episode of the disease occurred, but recovery was achieved and the patient remained free of symptoms and laboratory changes associated with the disease. The disease course was regarded as polycyclic if the patient had more than one episode, but between relapses remission was achieved (relapsing-remitting disease). A chronic-progressive course was defined by a partial response to therapy with failure to achieve remission 24 months after the diagnosis.

The disease course and response to treatment were assessed by physical examination and changes in the levels of serum muscle enzymes. Remission was defined as: (i) stable improvement or normalization of muscle strength, (ii) normalization of serum CK and/or LDH activity, and (iii) the disappearance of cutaneous changes. A relapse was defined as disease reactivation after a remission lasting 6 months or more.

Considering the retrospective and multicenter design of our study and the results of previously reported investigations, finding no correlation between relapses and disease severity (12), we decided not to assess the severitiy (activity) of the disease. While relapses can be develop after a prolonged disease-free interval, the probability of a monophasic course was determined in each case with only one episode of the disease.

Duration of follow-up and end-points

Data collection was terminated by April 1, 2003, when the present study was performed. The duration of follow-up was determined from time 0 corresponding to the date of diagnosis to either the date of death or to the date of the latest appearance at our departments (end-points). The median follow-up for patients with JDM was 32 months (range: 4.5 – 360.5; 25th percentile: 12.0 and 75th percentile: 69.4). Twelve patients were followed up for a minimum of 5 years out of our 38 JDM patients. None of the juvenile patients in our study have died. In the group of adult patients with primary DM, the median duration of follow-up was 78 months (range: 4–248; 25th percentile: 39 and 75th percentile: 107.43) for surviving patients. Nineteen adult patients were followed up more than 5 years and 6 adult patients were followed up more than 10 years. Four disease-related deaths occurred and the duration of follow up was 1.8, 3.45, 0.79 and 92.9 months for the patients who died due to DM. The causes of death were recorded in an autopsy (5 patients) or death certificate (1 patient).

Statistical analysis

Data were analyzed using the Statistica

6.0 statistics software. Probability of a monophasic clinical course and survival curves were drawn using the Kaplan-Meier method. The log-rank test was used to determine the statistical significance of the observed differences in survival rates between patient groups. We decided not to consider prognostic factors due to the fact that the number of events was insufficient to analyze the effect of any clinical features characteristic of DM on survival. Pvalues ≤ 0.05 were considered significant.

Results

Clinical characteristics of our DM patients

The clinical characteristics of our cohort of juvenile and adult DM patients are presented in Table II. There were more males than females in the group of juvenile patients. Extramuscular and extraskeletal manifestations of the disease were more frequent in adult patients. Only one JDM patient had ILD, and cardiac manifestations of the disease or respiratory muscle involvement were not observed in juvenile patients. Respiratory muscle involvement and ILD were more frequent among adult DM patients than the cardiac manifestation of the myositis.

Treatment and clinical course of our DM patients

Initially 37 JDM patients were treated with glucocorticoids. Twelve of them (20/37, 54.1%, CI: 36.9– 70.5%) responded to glucocorticoids and achieved remission, while 4/37 (10.8%, CI: 0.3 – 21.3%) patients received AZA during which time the glucocorticoid was tapered. 13/37 (35.1%, CI: 19.0–51.3%) were administered other second-line immunosuppressive agents and low dose glucocorticoids (in 6 cases with CYA and in 7 cases with MTX). Among these, 10 patients achieved remission while disease course of 3 patients became chronic. Only one patient was treated with intravenous immunoglobulin (IVIG). Data on this child was excluded from the analysis based on therapy.

In the group of adult DM patients, 20/35 (57.1%, CI: 39.3-73.7%) achieved remission on glucocorticoids alone. 15/35 patients (48.9%, CI: 26.3-60.6%) required additional immunosuppressive agents as initial therapy. 10/35 patients were administered glucocorticoids + CYA (among them, IVIG was also added in 4 cases, and in 1 case AZA was added). Two patients were treated with glucocorticoids and IVIG. One patient was given glucocorticoid and ritrosulfan (a Hungarian immunosuppressive drug, Lycurim) and 1 patient was treated with glucocorticoid + AZA. One patient was died, despite attempted treatment with the entire therapeutic arsenal (glucocorticoid, AZA, CYC, IVIG and plasmapheresis).

The disease course of 23/38 patients (54.8%, CI: 43.4 – 76.0%) with JDM was classified as monophasic (the probability of monophasic disease was 77-100%, median: 93%). 12/38 patients (31.6%, CI: 17.5 – 48.7%) had a polycyclic clinical course and 3/38 patients (7.9%, CI: 1.6-21.3%) had chronic disease. In the group of 35 patients with adult DM, 18 (51.4%, CI: 33.9-68.6%) patients had monophasic disease (the probability of monophasic disease was 63-100%, median: 81%); 13 (37.1%, CI: 21.5 – 55.1%) had polycyclic disease; one (2.9%, CI: 0.07 – 14.9%) had chronic disease; and 3 (8.6%, CI: 1.8-23.1%) had acute fulminant myositis.

Difference between initial treatment regimens

To investigate the difference between the initial treatment and that following disease course, we divided patients into two groups based on which therapy led to remission: glucocorticoid alone or glucocorticoid and second-line immunosuppressive agent(s).

Twelve of 37 patients with JDM (54.1%, CI: 36.9 – 70.5%) were administered glucocorticoids, which led to remission. In this group, 12/20 (60%, CI: 36.1 – 81.0%) children had monophasic disease (the probability of monophasic disease: 61-100%, median: 100%), and 8/20 (40%, CI: 19.1-64.0%) had polycyclic disease (number of relapses: 1-4, mean: 1.9).

Seventeen of 37 JDM patients received second-line immunosuppressive agents with glucocorticoids as the initial treatment. Among these patients, 10/17 (58.8%, CI: 33.0-81.5%) had monophasic (the probability of monophasic disease: 79-100%, median: 83.5%), 4/17 (23.5%, CI: 6.8-50.0%) had polycyclic (number of relapses: 1-2, mean: 1.25) and 3/17 (17.7%, CI: 38.0-43.4%) had chronic disease.

Among adult DM patients requiring only glucocorticoids as the initial treatment, 12/20 cases of monophasic (60%, CI: 36.1-80.8%, the probability of monophasic disease: 65-100%, median: 81%) and 8/20 cases of polycyclic (40%, CI: 19.1-63.9%, number of relapses: 1-8, mean: 3.25) disease were observed. In the second group, where second-line immunosuppressive agents were required, 3/15 patients (20%, CI: 4.3-48.1%) had acute fulminant myositis; 6/15 patients were monophasic (40%, CI: 16.3-67.7%, the probability of monophasic disease: 63-100%, median: 78%); 5/15 patients were polycyclic (33.3%, CI: 11.8-61.6%, number of relapses: 1-3, mean: 2.2); and 1/15 patients had chronic disease (6.67%, CI: 0.01-31.9%).

Table II. Demographic and clinical features of our patients with juvenile (JMD) or adult dermatomyositis (DM).

	JDM	DM
Number of patients	38	35
Mean age at the time of dignosis	8.6 yrs. (3-16)	44.0 yrs. (22-71)
Male:female ratio	1:1.7	1:2.5
Median duration of follow up time	32 month (4.5-360.5)	78 month (4.0-248.0)
ILD	2.4% (0.07-13.8%)	22.8% (CI: 10.4-40.1%)
Respiratory muscle involvement	0%	17.1% (CI: 6.6-33.5%)
Cardiac manifestation	0%	8.6% (CI:1.8-23.1%)

JDM: juvenile dermatomyositis; DM: dermatomyositis; ILD: interstitial lung disease; CI: confidence interval.

Relapse rate of our DM patients

A polycyclic (remitting-relapsing) disease course was observed in 12/38 juvenile patients (31.6%, CI: 17.5-48.6%) and in 13/35 adult DM patients (37.1%, CI: 21.4-55.1%). We plotted the cumulative relapse-free proportion of patients against the follow-up time using the Kaplan-Meier method. As shown in Figures 1 and 2, the relapse rate of the disease during the first year after the first remission had been achieved was higher than later in the course. Among JDM patients with a polycyclic disease course, the longest disease-free interval after first remission had been achieved was 24 months, while this interval was 86 months in the group of adult DM patients. In other words, among JDM patients relapses did not develop after a 24-month disease-free interval and patients remained in remission.

Survival of our DM patients

None of the juvenile patients in our study, but 6 patients in our cohort of adult DM patients died. Nevertheless, the survival probability was not significantly different between JDM and adult DM patients (Fig. 3). In the group of adult DM, 1-, 5- and 10-year survival rates were 91.4% (CI: 82.6-100%), 91.4% and 84.9% (CI: 71.1-100%), respectively. There were 4 disease-specific deaths at the age of 28, 49, 54, 61 years, after 1.8, 3.45, 0.79 and 92.9 months of follow-up. Among those patients who died due to disease-related causes, 2 died within 12 months after the diagnosis and only 1 patient died more than 5 years after the diagnosis of myositis was made. The F:M ratio of cases ending in mortality was not similar to the F:M ratio for the disease itself: 3 were male and only 1 was female. Causes of death were cardiac and pulmonary complications (2 cases of acute heart failure and 2 cases of respiratory muscle involvement). Non-disease specific causes of death were viral meningitis and liver failure.

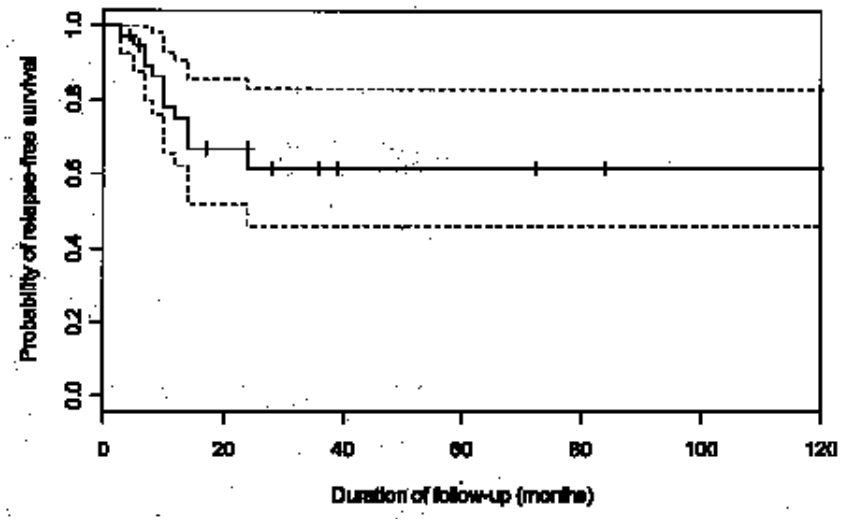

Fig. 1. Proportion of juvenile patients with dermatomyositis in remission without relapses, with 95% confidence intervals.

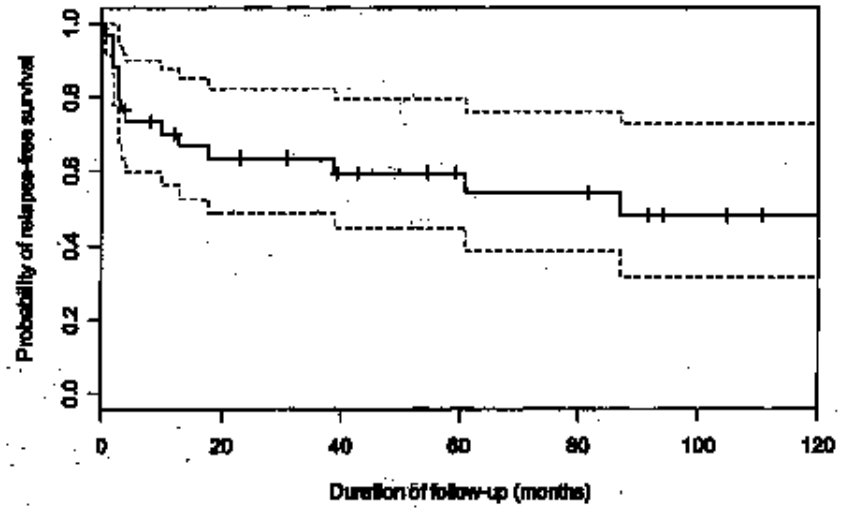

Fig. 2. Proportion of adult patients with dermatomyositis in remission without relapses, with 95% confidence intervals.

Discussion

We report the first study on the disease course, relapse rate and survival of patients with JDM who were diagnosed, treated and followed up in Hungary. The clinical characteristics of our cohort of juvenile and adult DM patients (distribution of different types, female to male ratio, age distribution) were similar to those in other series in the literature (7, 9, 17).

We found that most of the juvenile and adult patients with DM had a monophasic disease course. The frequency of the polycyclic (relapsing-remitting) disease course was similar in both groups of patients. A chronic disease course was more frequent among JDM patients. Huber and colleagues studied 65 JDM patients and found that 24 (37%) patients had a monocyclic course and 41 (63%) had a chronic continuous or polycyclic course (6). Phillips *et al*. observed a similar frequency of relapses in adults (50-60%) (12).

As shown in Figures 1 and 2, the risk of relapse was higher during the first year after remission than later in the disease course in both the juvenile and adult patients. Among adult patients, relapses were found to be more frequent within the first 24 months after the diagnosis of the disease (12). According to our results and the literature data, we must emphasize that patients with JDM should be followed up for at least 2 years even if they are in remission. In our study, 11 of 24 JDM patients with monophasic disease were followed up for less than 24 months. All of them

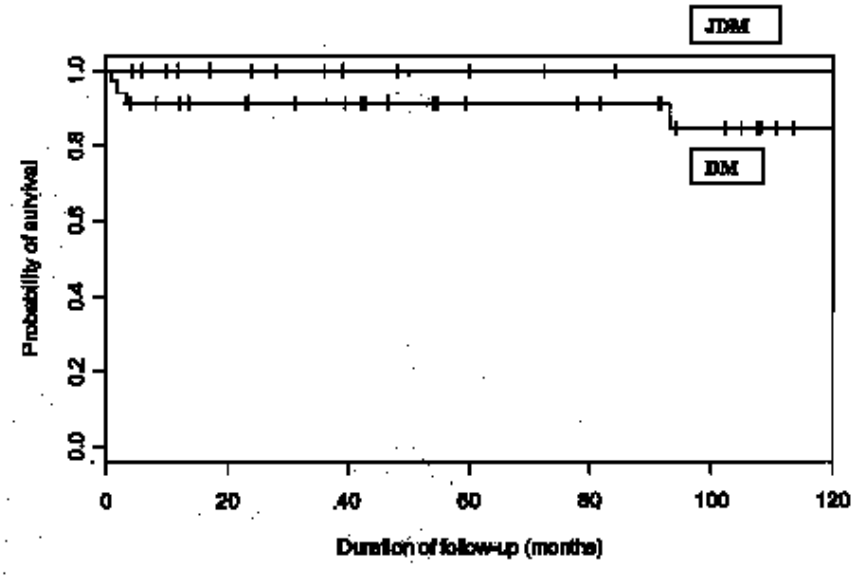

Fig. 3. Survival curves of patients with juvenile or adult dermatomyositis, with 95% confidence intervals. JDM: juvenile dermatomyositis; DM: adult dermatomyositis.

were in remission when the follow-up period came to an end and we assume that in the majority of cases this was due to a complete recovery.

All of the children were given glucocorticoids initially, except for one who received IVIG. 20/38 (52.6%) patients achieved remission due to classical glucocorticoid therapy, while 18/38 (47.4%) patients required second-line agents. This ratio does not differ considerably from the data available in the literature: 62/65 (95%) patients were treated with glucocorticoids, while 42/65 (63%) received a second-line agent in Huber's cohort of patients (6). The frequency of a monophasic disease course was the same among juvenile and adult patients who received second-line immunosuppressive agents initially, and among juvenile or adult patients who were given glucocorticoids alone. As previously reported by others, there is no evidence of a correlation between the occurrence of relapses and the initial severity of the disease or the mean starting dose of glucocorticoids (10,12). In this study, we observed no correlation between the initial therapeutic regimen (glucocorticoid alone, or with second-line immunosuppressive agents) and subsequent relapses.

Survival studies are influenced by several factors which can modify the results considerably, and the observed differences in mortality rates are attributable to: (i) the way patients are selected (diagnostic criteria, recruitment from a single or more than one center, which subgroups of IIMs are included in the analysis), (ii) whether a sufficient number of patients have been recruited and whether data from cases lost to follow-up are included or not, and (iii) the duration of follow-up. Available data on the survival of patients with IIMs come from the USA, England, France, and Israel (Table III). Clinicopathological subgroups of IIMs included in these studies differ considerably. Therefore, our results are not exactly comparable with the data in the relevant literature. The relative size of the juvenile patient group was the largest in our study, but we studied only DM patients. It is also important to mention that patients with CAM and overlap myositis were excluded. With all of these considerations in mind, our study indicates that patients with juvenile and adult DM showed survival rates similar to those reported in the international literature. We found no significant difference between the adult and juvenile patient groups. The major causes of death were similar to those reported by others (5, 18).

In conclusion, no correlation was found between relapse-free survival and the initial therapeutic regimen. Considerable proportions of juvenile and adult DM patients have a polycyclic or chronic disease course and often require continuing medication and follow-up for many years. Based on our results, as relapses can occur after a prolonged disease-free interval, JDM and DM patients should be followed up for at least 2 years, even if they are in remission and have no signs and symptoms. Finally, although we found a favourable survival probability, further investigations are needed to assess functional outcome and quality of life.

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Table III. Survival of patients with idiopathic inflammatory myopathies in the literature.

	Location	Follow-up	No.	Clinicopathological subgroups	Survival rates		
					1-year	5-year	> 5-year
Maugars (1996)	France	1973-1984	69	PM, DM, JDM, OM, CAM	82.6%	66.7%	55.4% (9 yrs.)
Marie (2001)	France	1983-1998	77	PM, DM, CAM	83%	77%	61% (15 yrs.)
Sultan (2002)	England	1978-1999	46	PM, DM, JDM, OM	-	95%	83.8% (10 yrs.)
Present study (2003)	Hungary	1976-2003	35	JDM	100%	100%	-
Present study (2003)	Hungary	1976-2003	38	DM	91.4%	91.4%	84.9%

PM: polymyositis; DM: dermatomyositis; JDM: juvenile dermatomyositis; OM: overlap myositis; CAM: cancer-associated myositis.

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