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ORIGINAL RESEARCH

Postrehabilitation Functional Improvements in Patients With Inflammatory Myopathies: The Results of a Randomized Controlled Trial

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Abstract

Objective: To evaluate the medium-term functional effect and the effect on quality of life of a standardized rehabilitation program in patients with inflammatory myopathies (IMs).

Design: A multicenter, randomized controlled trial.

Setting: Four university hospitals.

Participants: Patients (N=21) with polymyositis.

Interventions: The intervention group participated in a 4-week standardized, hospital-based rehabilitation program followed by a personalized, self-managed, home-based rehabilitation program. The control group received physiotherapy on an outpatient basis. Study participants were evaluated at inclusion, at the end of the rehabilitation program (1mo), and then at 6 and 12 months.

Main Outcome Measures: The primary efficacy criterion was the Health Assessment Questionnaire Disability Index (HAQ-DI), and the secondary criteria were quality of life (according to the Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36] questionnaire), muscle performance (isokinetic strength, Motor Function Measure, and Kendall Manual Muscle Test), gait, pain, fatigue, and biomarkers of tolerance and disease activity.

Results: At 12 months, the mean ± SD HAQ-DI was significantly lower in the intervention group than in the control group (.64±.53 vs 1.36±1.02; $P=.026$). The intervention group also had better scores than the control group for some quality-of-life dimensions (SF-36 General Health: 53.44±8.73 vs 36.57±22.10, respectively; $P=.038$; SF-36 Role Physical: 63.89±43.50 vs 17.86±37.40, respectively; $P=.023$) and pain levels (5.0±10.61 vs 33.38±35.68, respectively; $P=.04$) at 12 months. The program was well tolerated by all the participants.

Conclusions: In patients with IMs, the combination of a 4-week standardized rehabilitation program and a personalized, home-based, self-managed rehabilitation program was well tolerated and had a positive medium-term functional effect.

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Polymyositis (PM) and dermatomyositis (DM) are rare inflammatory myopathies (IMs) that manifest themselves by impairments in proximal and axial striated skeletal muscles and a remitting-relapsing pattern of disease.[1,2] The estimated prevalence of PM/DM ranges from 0.6 to 11 per 100,000 people.[3,4] The clinical manifestations of PM and DM are caused by impairments of the proximal limb muscles, neck muscles, and pharyngeal muscles.[1,5] At present, the main treatment options for DM and PM are based on corticotherapy and immununosuppression.[6]

It is now well established that mechanical stress is able to modulate local inflammatory phenomena and cell differentiation.[7,8] The effect of rehabilitation on strength gains has been studied in many muscle diseases, including IMs.[9,10] In the latter conditions, the exercise-related gain in strength is due not only to better muscle microvascularization but also to the slowing of the inflammatory process in and around the muscle and to elevated mitochondrial enzyme activity.[11]

The published rehabilitation programs include aerobic exercise,[12] low-resistance strength training,[13-16] or both.[17] The most intensive protocol involved eccentric isokinetic strength training at 70% of the estimated 1-repetition maximum.[18] Hence, a body of evidence suggests that rehabilitation slows the clinical progression of IMs. However, the programs tested in the literature were focused on certain aspects of rehabilitation, such as the use of a relatively low intensity. We therefore decided to study the efficacy of a comprehensive, multidisciplinary rehabilitation program by taking account of the various aspects of PM and DM (notably functional ability and the various components of quality of life).

The primary objective of the present study was to assess the functional effect at 12 months of a standardized rehabilitation program in patients with IMs. The secondary objectives included assessments of quality of life, pain, and serum levels of inflammation markers.

Methods

We performed a Zelen randomized multicenter study (start of the inclusion period, March 1, 2008; study end, December 31, 2013). The trial compared a standardized rehabilitation/retraining program with standard care in a population of patients with IMs. Patients were recruited through the internal medicine departments at 4 university hospitals in France. The study was approved by the regional ethical committee for human research.

The inclusion criteria were as follows: (1) adult (aged >18y) patients with PM or DM according to the International Myositis Assessment and Clinical Studies Group criteria published by Dalakas and Hohlfeld[19]; (2) Health Assessment Questionnaire Disability Index (HAQ-DI) of ≥0.5; (3) recent, ongoing relapse (whether the first relapse or a recurrent relapse); (4) decrease in muscle strength of ≥20 percentage points on a scale of 0 to 100 (where 100 corresponds to the score of an unaffected subject); and (5) muscle pain visual analog scale score of ≥30 out of 100.

The exclusion criteria were as follows: (1) absence of a recent relapse (ie, >6 mo previously); (2) concomitant presence of another chronic, invalidating disorder (a disease that causes disability); (3) progressing cancer; (4) cognitive disorders or lack of fluency in French; (5) inability to give informed consent; (6) participation in a standardized rehabilitation program in the 6 months before inclusion; and (7) ongoing or recent (<3mo previously) participation in another therapeutic trial.

Our use of the Zelen design[20] (ie, postrandomization consent) was justified because the evaluation of rehabilitation programs poses specific methodological issues; these notably include the absence of a placebo intervention and the inability to blind the patient or the therapist to the nature of the intervention.

All eligible patients had initially been invited to participate in a study of disability in patients with PM or DM. After randomization, the patients in the intervention group were invited to take part in the rehabilitation study. Patients who agreed to participate therefore gave their informed, written consent a second time. Patients in the control group were not told about the rehabilitation protocol and received standard treatment. The study schedule was as follows: an inclusion visit, an initial visit for the intervention group, and then 3 follow-up visits (1, 6, and 12mo after inclusion) (fig 1).

In the intervention group, a personalized rehabilitation program was focused on muscle strength training, chest expansion, increased joint range of motion, better gait and transfers, and improved aerobic capacity. Strength training was performed (at 60% of the estimated 1-repetition maximum) for muscles with a Medical Research Council Scale score of at least 3 out of 5, with 2 series of 10 repetitions per day. For respiratory rehabilitation, patients performed 20 minutes of inspiratory and expiratory muscle strength training. Joint range of motion was trained by passive movements and stretching exercises. Walking ability was trained in a 30-minute walk. Patients performed 30-minute sessions of aerobic exercise on a cycle ergometer 3 times a week (at 60% of the estimated maximum heart rate) and also received three 30-minute massage and relaxation sessions a week. Patients with pharyngeal muscle weakness performed swallowing exercises. In the subsequent home-based, self-managed rehabilitation program, each participant performed a daily 30-minute session derived from the hospital-based program.

Although patients in the control group did not participate in the rehabilitation program, the attending physicians prescribed 30-minute sessions with a private practice physiotherapist 3 times a week.

None of the raters were involved in the rehabilitation program. All the raters had been trained in the study's efficacy criteria by the investigators.

Efficacy criteria

The study's primary efficacy criterion was the French-language version of the HAQ-DI rated 12 months after inclusion.[21] The HAQ-DI ranges from 0 (no functional disability whatsoever) to 3 (severe functional disability).[22] The HAQ-DI was first translated into French and validated (in rheumatoid arthritis) in 1992.[23]

Secondary criteria

Quality of life was evaluated with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) questionnaire.[24] In patients with PM and DM, the HAQ-DI is strongly correlated with

List of abbreviations:

CPK	**creatine phosphokinase**
DM	**dermatomyositis**
HAQ-DI	**Health Assessment Questionnaire Disability Index**
IM	**inflammatory myopathy**
MMT	**Manual Muscle Test**
PM	**polymyositis**
SF-36	**Medical Outcomes Study 36-Item Short-Form Health Survey**

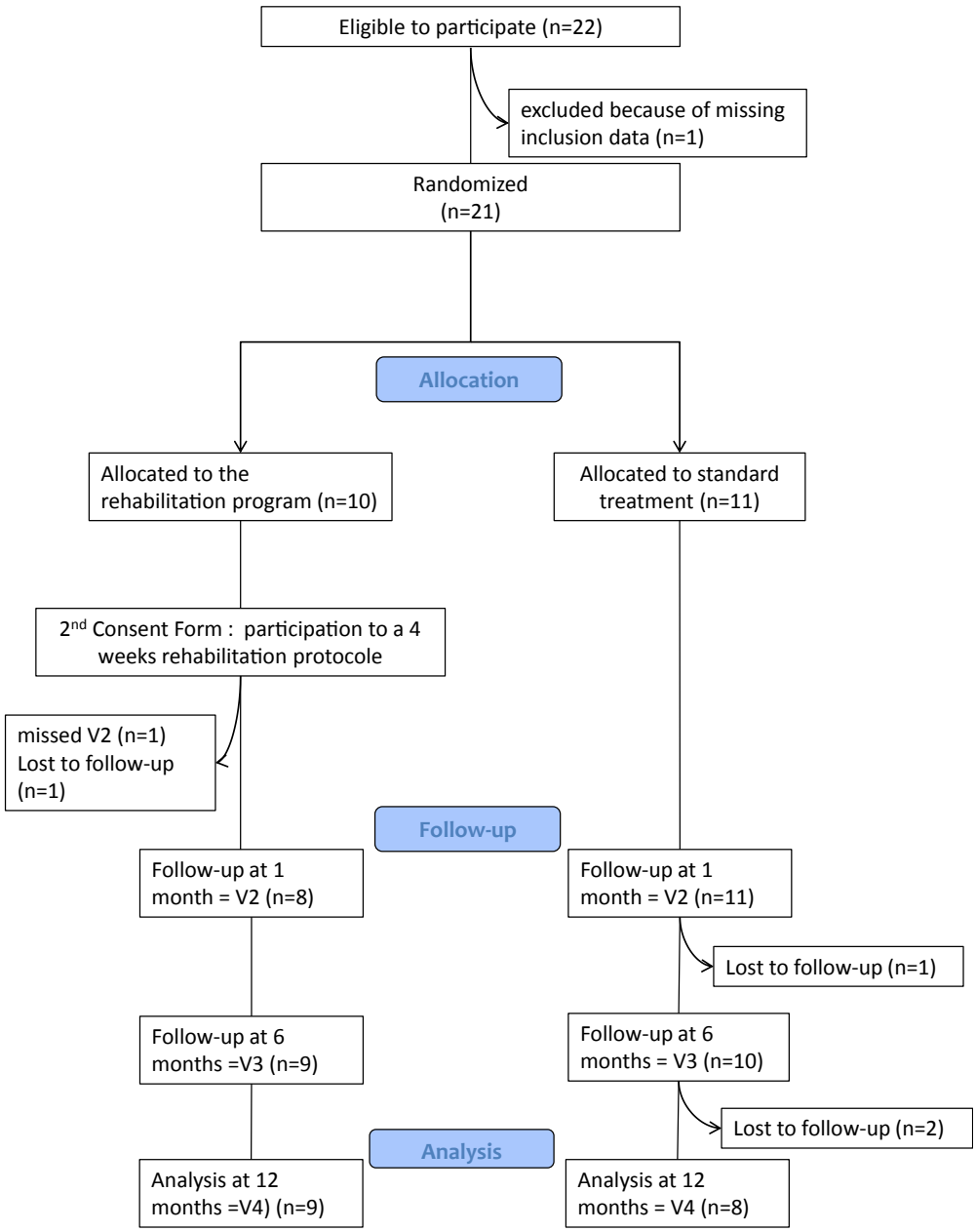

Fig 1 Flowchart. Abbreviations: V2, visit at 1mo; V3, visit at 6mo; V4, visit at 1y.

the functional domain of the SF-36 ($r=-.71$).[21] The SF-36 is easy to administer and has already been used in studies of myositis.[15,21,25-27]

The Kendall Manual Muscle Test (MMT)[28] has been selected by the International Myositis Assessment Clinical Studies Group for the evaluation of patients with PM and DM. It is based on the sum of scores on an 11-point scale (ranging from 0 to 10) for 10 muscle groups; the maximum (best possible) score is 100.

The Motor Function Measure is a validated, quantitative scale developed in 2005 for use in patients with neuromuscular diseases (such as DM and PM).[29]

Isokinetic assessments of the knee flexor and extensor muscles were performed using a Con-Trex dynamometer.[30,a]

Two 0-to-100 visual analog scales were used to assess pain and fatigue. Patients were asked to rate their level of pain on a 100-mm line between 0 (no pain/no fatigue) and 100mm (the worst pain imaginable/extreme fatigue).

We evaluated the distance covered in a 6-minute walk test.[31,32]

Lastly, serum C-reactive protein and creatine phosphokinase (CPK) levels were assayed at each visit.

Statistical analysis

Our starting hypothesis was that 60% of patients in the intervention group and 30% of the patients in the control group would have an HAQ-DI of <0.5. With a 2-tailed test and an alpha risk of 5%, the target sample size was calculated to be 45 participants per group (yielding a power of 85%).

Given that we did not achieve our recruitment target, we decided to observe the changes in the study parameters at different

Table 1 Description of study population

Characteristics	Intervention Group (n=10)	Control Group (n=11)	*P*
Sex (M/F)	4/6	3/8	.085
Age (y)	51.9±9.85	57.63±15.47	.099
Duration of disease (mo)	45.67±40.65	60.45±76.30	
CRP (mg/L)	5.67±4.80	9.97±20.78	.941
CPK (IU/L)	258.55±260.61	329.8±416.84	.085
HAQ-DI	1.22±0.38	1.36±0.80	.918
MFM			
D1	76.62±16.54	61.12±28.51	.251
D2	96.66±3.42	81.71±18.92	.016
D3	95.24±5.02	84.59±27.8	.973
Total	88.33±7.06	79.64±18.10	.512
Kendall MMT			
Right	82.50±8.67	72.18±14.84	.72
Left	82.2±6.32	70.80±17.46	.133
6MWT (m)	381.44±84.35	374.24±164.97	.882
Fatigue VAS	56.20±31.90	40.82±31.90	.314
Pain VAS	36.10±37.11	28.59±2 5.17	.918
SF-36			
Physical scores			
SF-36 PF	45.5±21.53	36.82±28.92	.387
SF-36 RP	25±28.87	40.91±39.17	.468
SF-36 BP	49.9±25.36	47.9±20.80	.918
SF-36 GH	42.1±14.69	40±15.46	.918
Mental scores			
SF-36	41±14.68	41.82±19.66	.863
SF-36 SF	60±26.22	55.68±28.15	.863
SF-36 RE	49.9±25.36	47.9±20.80	.197
SF-36 MH	55.2±20.46	53.82±19.3	>.99

NOTE. Values are n, mean ± SD, or as otherwise indicated.
Abbreviations: 6MWT, 6-minute walking test; BP, Bodily Pain; CRP, C-reactive protein; D1, dimension 1: standing position and transfer; D2, dimension 2: axial and proximal motor function; D3, dimension 3: distal motor function; F, female; GH, General Health; M, male; MFM, Motor Function Measure; MH, Mental Health; PF, Physical Functioning; RE, Role Emotional; RP, Role Physical; SF, Social Functioning; VAS, visual analog scale.

time points. Qualitative variables were reported as the number (percentage), and quantitative variables were reported as the mean ± SD. The normality of data distribution was checked graphically and by applying the Shapiro-Wilk test. The degree of similarity between the groups at inclusion was assessed using a Mann-Whitney test. We used a mixed linear model (covariance structure) with repeated measures to compare the study groups in terms of the measurements at each time point. Choice of the covariance model was based on the Akaike information criterion. The normality of the residuals was checked, and the data were log-transformed if the distribution was non-Gaussian. In view of the small sample size, the result was not adjusted for multiple comparisons. In all statistical tests, the threshold for statistical significance was set to $P<.05$. All analysis were performed with SAS software (version 9.4[b]).

Results

Description of study population

Between April 1, 2008, and June 30, 2011, 21 patients were included after the inclusion visit (10 participants in intervention group, 11 participants in control group). One patient in the intervention group withdrew from the study before V2 (visit at 1 month), and 1 patient in the intervention group missed the evaluation at V2. In the control group, 1 patient withdrew from the study between V2 and V3 (visit at 6 months), and 2 patients withdrew between V3 and V4 (visit at 1 year).

Table 1 summarizes the characteristics of the study population at inclusion. According to the diagnosis criteria, all patients had a diagnosis of PM. All the patients were taking corticosteroids (prednisone, 5−10mg/d); 3 patients in the control group were taking methotrexate, and 1 patient in the intervention group was taking azathioprine. Three patients (2 in control group, 1 in intervention group) had received intravenous immunoglobulins >3 months before inclusion.

The groups were similar in terms of sex ratio, age, disease duration, clinical biochemical parameters (platelet count and serum hemoglobin, C-reactive protein, and CPK levels), HAQ-DI, the SF-36 subscores, the Kendall MMT scores on the right and left sides, the isokinetic evaluation of knee flexor and extensor strength, distance in the 6-minute walk test, and pain and fatigue visual analog scale scores. However, the groups differed significantly when considering one of the Motor Function Measure subscores; the D2 score (axial and proximal motor function) was worse in the control group than in the intervention group (81.71±18.92 vs 96.66±3.42, respectively; $P=.016$).

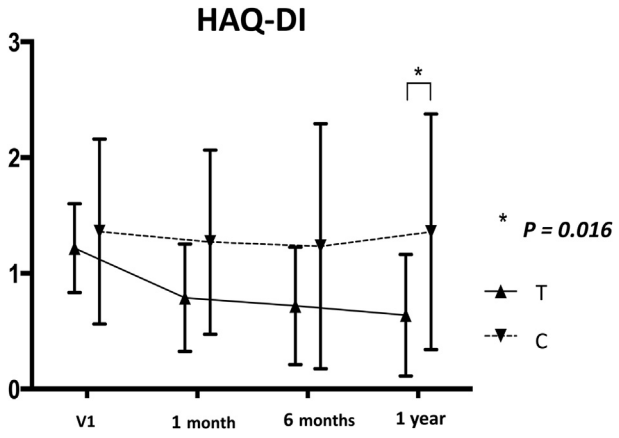

Fig 2 Mean HAQ-DI scores in treated patients (T) and controls (C) at V1, 1 month, 6 months, and 1 year. *Indicates $P = .016$. Abbreviation: V1, visit 1 at inclusion.

Analysis of criteria

The sample size prevented us from verifying the starting hypothesis (60% of patients in intervention group and 30% in control group with an HAQ-DI score <0.5). Nevertheless, 5 (50%) of the 10 patients in the intervention group and 2 (18%) of the 11 patients in the control group had an HAQ-DI score <0.5 at 12 months. The change over time in the HAQ-DI is shown in figure 2. At 12 months (V4), the HAQ-DI was significantly lower in the intervention group than in the control group (.64±.53 vs 1.36±1.02; $P=.016$). There were no significant intergroup differences at the other assessment time points.

At the follow-up assessment at 1 year, the SF-36 Role Physical subscore was significantly higher in the intervention group than in the control group (63.89±43.50 vs 17.86±37.40; $P=.023$). The General Health subscore was also significantly greater in the intervention group than in the control group at 1 year (53.44±8.73 vs 36.57±22.10; $P=.038$) (fig 3A).

Figure 3B shows the change over time in the SF-36 mental subscores. The Vitality subscore was significantly greater in the intervention group than in the control group at 1 month (46.67±16.77 vs 33.57±25.28; $P=.048$) but not at 6 months (V3; $P=.08$) or 12 months (V4; $P=.09$). The Role Emotional subscore was significantly greater in the intervention group than in the control group at 1 month (55.56±40.83 vs 47.41±42.42; $P=.03$). There were no significant intergroup differences in the other SF-36 mental subscores (Mental Health, Social Functioning) at any time point.

There were no significant intergroup differences in the Motor Function Measure scores at any time point.

At 1 year, the Kendall MMT score was higher on the left side in the intervention group than in the control group (85.89±16.11 vs 65.22±31.50; $P<.05$). The change in muscle strength on the right side was not significant at 6 months ($P=.055$) or 1 year ($P=.07$) (fig 4).

There were no intergroup differences in total work or the peak isokinetic torque for the knee flexors and extensors (at 60°/s or 120°/s) at any of the time points.

At 12 months, pain levels were significantly lower in the intervention group than in the control group (5.0±10.61 vs 33.38±35.68; $P=.04$).

The level of fatigue was similar in the 2 groups at all evaluations. The results of the 6-minute walk test did not differ when comparing the groups at any of the time points. Lastly, there were no intergroup differences in the C-reactive protein or CPK levels.

Discussion

The objective of the present study was to evaluate the putative benefit of a 4-week, multidisciplinary, hospital-based rehabilitation program on perceived disability and clinical manifestations in patients with IMs. Although our starting hypothesis could not be verified, our study revealed positive effects of this rehabilitation program at 6 months and 1 year, when considering the HAQ-DI and physical and mental aspects of quality of life (SF-36).

Earlier clinical trials mainly investigated the effects of laboratory-based exercise or endurance training at submaximal or (more recently) high intensity.[33-35] In a recent literature review, Alemo Munters et al[33] listed 8 controlled therapeutic trials that had demonstrated the efficacy of a physical exercise program in PM and DM.[34,36-38] The exercises were supervised by a therapist, with the exception of the recent trial by Alexanderson et al[34] in which a group performing resistive home exercises was compared with a group performing active movements only.

Exercise programs are associated with a biological effect, as evidenced by elevated mitochondrial enzyme activity, increased capillary density, and better aerobic performance (maximum oxygen consumption), and the absence of harmful effects (CPK elevation and inflammation).[39,40]

Benefits in terms of functional ability and quality of life have been evaluated with the SF-36 questionnaire, the Instrumental Activities of Daily Living score, and the International Myositis Assessment Clinical Studies index.[33] A 2014 study[38] of 3 patients with PM highlighted an improvement in the SF-36 scores and the HAQ-DI after a 12-week supervised rehabilitation program.

Our study highlights a significantly better HAQ-DI in the intervention group at 12 months. Our results reinforce the concept whereby rehabilitational care in patients with PM or DM improves their functional ability and quality of life. The results for the mental dimension of the SF-36 score underline the importance of providing patient support. As with the SF-36 vitality subscore at 1 month, patients in the intervention group (hospital-based rehabilitation) had a higher emotional dimension (Role Emotional) score than controls at 1 month, but not at 6 and 12 months.

We noted an improvement in the Kendall MMT score at 12 months in the intervention group for the left side. The left side improvement has to be considered with caution since the right side showed no significant improvement.

As expected, pain levels were also significantly reduced in the intervention group.[35] These improvements suggest that a 4-week, comprehensive, standardized, hospital-based rehabilitation program is enough to improve strength and reduce pain levels. The duration of supervised care in the present study (4wk) is somewhat shorter than those described in the literature. However, our hospital-based program was followed by a home-based program.

Our work did not find any significant changes in CPK or C-reactive protein levels in either of the 2 groups of patients, so the program was well tolerated in the intervention group.

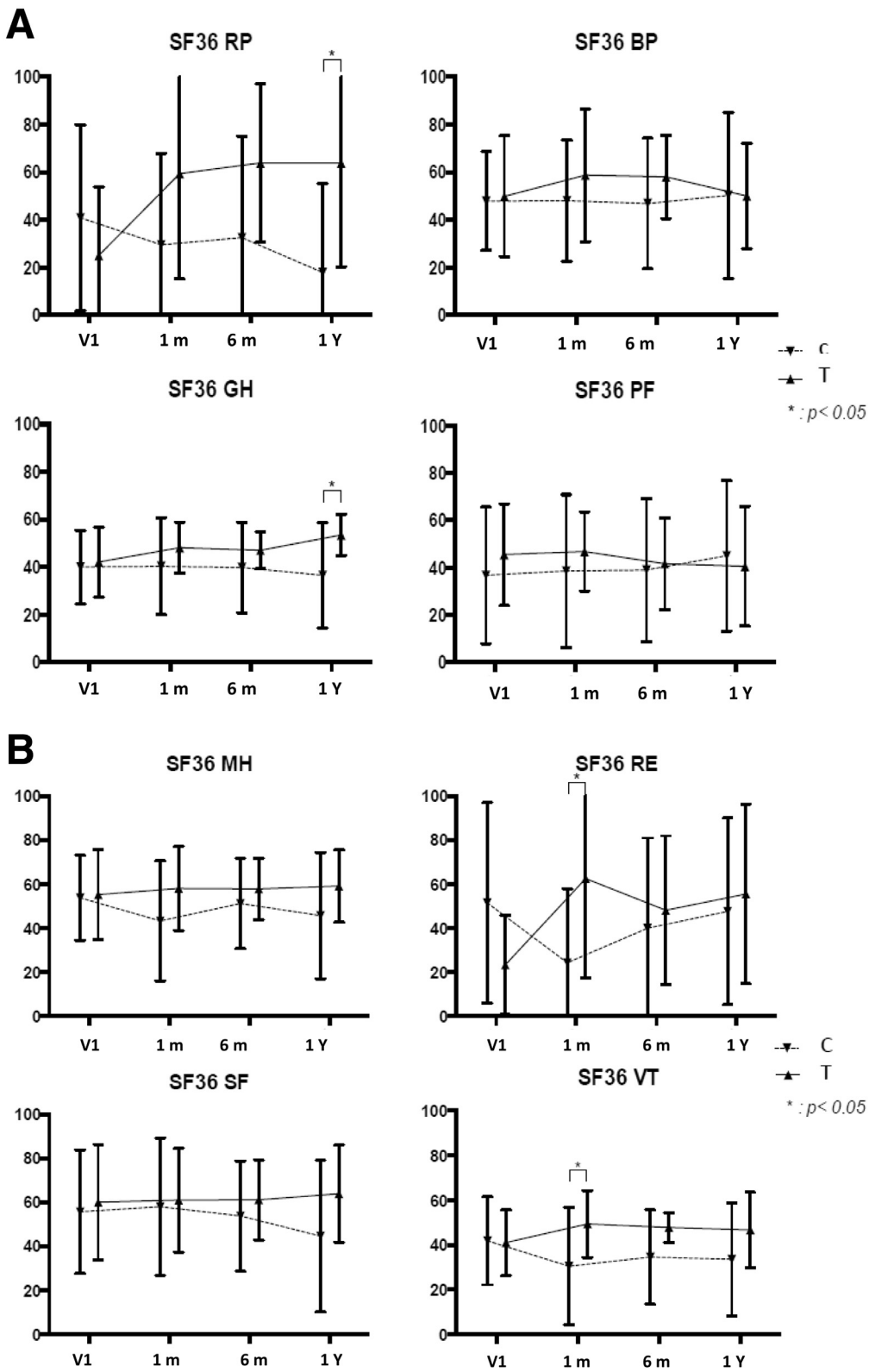

Fig 3 (A) Mean SF-36 physical scores in treated patients (T) and controls (C) at V1, 1 month, 6 months, and 1 year. (B) Mean SF-36 mental scores in treated patients (T) and controls (C) at V1, 1 month, 6 months, and 1 year. *Indicates $P < .05$. Abbreviations: BP, Bodily Pain; GH, General Health; MH, Mental Health; PF, Physical Functioning; RE, Role Emotional; RP, Role Physical; SF, Social Functioning; V1, visit 1 at inclusion; VT, Vitality.

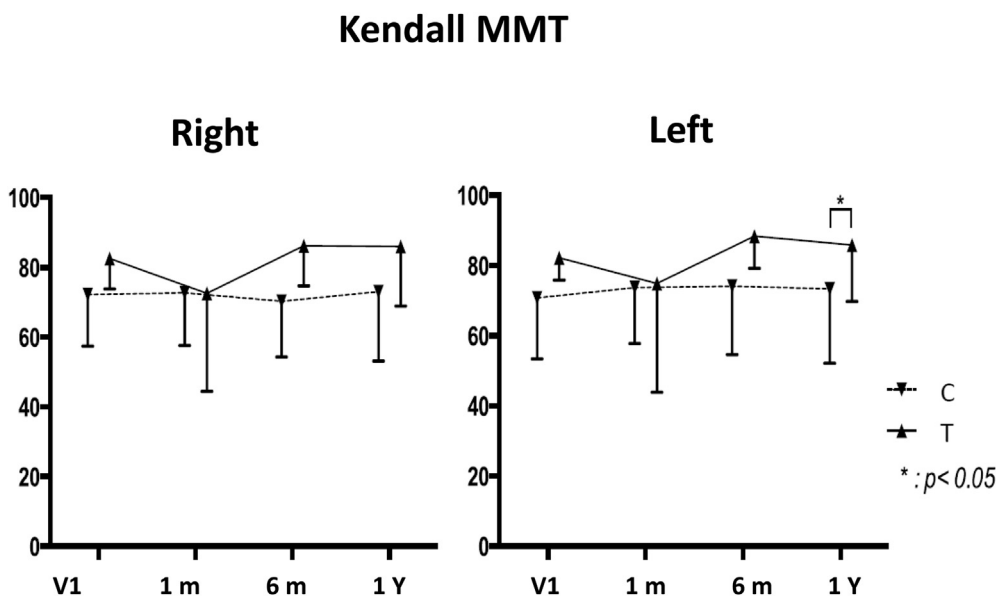

Fig 4 Mean Kendall testing scores (based on the sum of scores on an 11-point scale, ranging from 0 to 10) for 10 muscle groups (the maximum score is 100) in treated patients (T) and controls (C) at V1, 1 month, 6 months, and 1 year. *Indicates $P < .05$. Abbreviation: V1, visit 1 at inclusion.

Our present observations argue in favor of the generalization of this type of care. A standardized, comprehensive, hospital-based program followed by personalized, self-managed, home-based exercises appears to be optimal for a disease in which the degree of impairment can vary markedly from 1 individual to another.

Study limitations

The present study had some limitations. First, the small sample size was responsible for a lack of statistical power. Our recruitment problems were because PM and DM are rare diseases that require monitoring in a reference center. Furthermore, other clinical trials (with exclusion periods) were being carried out at the same time in our centers. Second, because of multiple testing issues, we cannot exclude false-positive findings, and results should be interpreted with caution.

Even though the disease duration was essentially the same in the 2 groups, the time interval between the first symptoms and the diagnosis was not recorded and might thus constitute a source of bias.

Our program included a period of home-based, self-managed rehabilitation; however, this rehabilitation was not supervised. Therefore, adherence to the program could not strictly be assessed, and the effect on the results is uncertain. It may be that only motivated patients agreed to participate in the study; if so, the study population would have differed from that seen in clinical practice. In the future, it will be interesting to study the level of compliance with the home-based exercises. Compliance with this part of the rehabilitation program could be boosted by organizing regular, individual face-to-face or telephone interviews. The difficulty of implementing a true placebo intervention in this type of study prompted us to adopt Zelen's design. Even though this method appears to be the most appropriate for a randomized controlled trial, it can never totally rule out bias related to the lack of blinding.

Conclusions

In patients with IMs, we compared a standardized, hospital-based rehabilitation program followed by home-based exercises with home-based physiotherapy. Function and quality of life were better at 12 months in the treated group, although a larger sample size would be needed to assess the program's superiority.

Suppliers

a. Con-Trex isokinetic dynamometer; CMV AG.
b. SAS software (version 9.4); SAS Institute, Inc.

Keywords

Myositis; Quality of life; Rehabilitation

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