RHEUMATOLOGY

Rheumatology 2011;50:2113–2124
doi:10.1093/rheumatology/ker292
Advance Access publication 2 September 2011

Original article

Safety and efficacy of exercise training in patients with an idiopathic inflammatory myopathy—a systematic review

Gerarda E. A. Habers[1,2] and Tim Takken[1]

Abstract

Objective. Idiopathic inflammatory myopathies (IIMs) are a group of rare heterogeneous autoimmune skeletal muscle disorders characterized by muscle weakness, excessive muscle fatigue and diminished aerobic fitness. Exercise training could be one way to prevent or delay the negative effects of the disease and the impairments seen in patients with an IIM. The objective was to examine whether exercise training is safe and effective in patients with an IIM.

Methods. All experimental studies that assessed the safety and/or efficacy of an exercise training programme in patients with an IIM except for case studies were reviewed. Pre-MEDLINE, MEDLINE and EMBASE database searching was done up to November 2010. Information was extracted on the number of participants, characteristics of participants, type of intervention, type of outcome measure, type of study design, report characteristics, geographical origin and risk of bias within studies. The change (percentage and significance) in group mean or median for each outcome measure in each study was determined as well.

Results. Two randomized controlled trials, one non-randomized controlled trial and nine uncontrolled trials were included. No studies in children were found. Safety measures did not worsen and efficacy measures improved or did not change. Most of the included studies had a high selection and/or allocation bias.

Conclusions. In conclusion, it appears that exercise training is safe and effective in adult patients with active as well as inactive stable IIMs. However, more studies with a well-controlled design are needed. In addition, studies in children with an IIM are indicated.

Key words: Exercise training, Idiopathic inflammatory myopathies, Efficacy, Safety, Systematic review.

Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of rare heterogeneous autoimmune skeletal muscle disorders. IIMs can be broadly subdivided into three main subtypes: DM, PM and IBM that can all be characterized by muscle weakness and inflammatory infiltrates in muscle biopsies. The three subtypes of IIM differ from each other in, among others, the age of onset, the location of muscle involvement and the responsiveness to medical treatment. DM and PM affect both children and adults; IBM occurs only in adults. Patients with IBM show mainly muscle weakness in the wrist and finger flexors and in the quadriceps muscles. However, patients with DM and PM show mainly muscle weakness at the proximal muscles of both the upper and lower extremities. In DM, the skin is involved as well. Patients with PM and DM respond to drug therapy, while patients with IBM are resistant to it [1].

Muscle inflammation, secondary metabolic disturbances (e.g. reduced ATP and creatine phosphate levels [2, 3] and capillary blood supply [4] in muscle tissue), steroid treatment-induced myopathy [5], cardiac abnormalities [6], pulmonary involvement [7] and physical inactivity can all play a role in one or more of the following

[1]Child Development and Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands and [2]Faculty of Human Movement Sciences, VU University Amsterdam, Amsterdam, The Netherlands.

Submitted 18 February 2011; revised version accepted 14 June 2011.

Correspondence to: Tim Takken, Child Development and Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, Room KB2.056.0, PO Box 85090, 3508 AB Utrecht, The Netherlands. E-mail: t.takken@umcutrecht.nl

impairments seen in patients with an IIM: muscle weakness, excessive muscle fatigue and diminished aerobic fitness [8]. These impairments can subsequently lead to disabilities such as problems with walking and manual control. Exercise training could be one way to prevent or delay these negative effects of the disease and thus possibly reduce the disabilities seen in patients with an IIM. However, in the past, exercise training was discouraged in patients with an active IIM because it was thought it might worsen the inflammatory process [9]. At present, indications of beneficial effects without disease exacerbations with exercise training have been found [10, 11]. Exercise training may not only delay the progression of the disease or prevent a poor outcome, but it could also decrease the risk of cardiovascular diseases as is observed in healthy subjects [12, 13].

The objective of this systematic review was to examine whether exercise training is safe and effective in patients with an IIM. For this purpose, all experimental studies that assessed the safety and/or efficacy of an exercise training programme in these patients except for case studies were reviewed. Furthermore, a summary of the training programmes used in this population is given.

Materials and methods

Eligibility criteria

Types of report

No publication date or publication status restrictions. Only English-language reports were included.

Types of study design

All experimental studies except for case studies.

Types of participants

Patients with PM, DM or IBM with any stage of the disease, including children and adults.

Types of intervention

Exercise training was defined as muscle strength training and/or aerobic training (possibly combined with another type of intervention) at home or in combination with training on site for at least 3 weeks, 2 days a week and 20 min each time. Within these criteria, exercise training programmes of all intensities, frequencies and durations were considered.

Types of outcome measures

All outcome measures related to safety or efficacy were included.

Information sources

Studies were identified by searching electronic databases, scanning reference lists of included reports and tracking forward citations of included reports. The electronic database searching was applied to Pre-MEDLINE, MEDLINE and EMBASE. Relevant terms describing exercise training and IIMs were used. No publication date or publication status restrictions were imposed on the search strategy. Details of the search strategy are described the supplementary section 1, available as supplementary data at *Rheumatology* Online. The last search was run on 19 November 2010.

Study selection

Two reviewers performed eligibility assessment in an unblinded standardized manner. A detailed explanation of the study selection methods is described in the supplementary section 2 (Methods), available as supplementary data at *Rheumatology* Online. A summary of the study selection process is depicted in Fig. 1.

Data collection process and data items

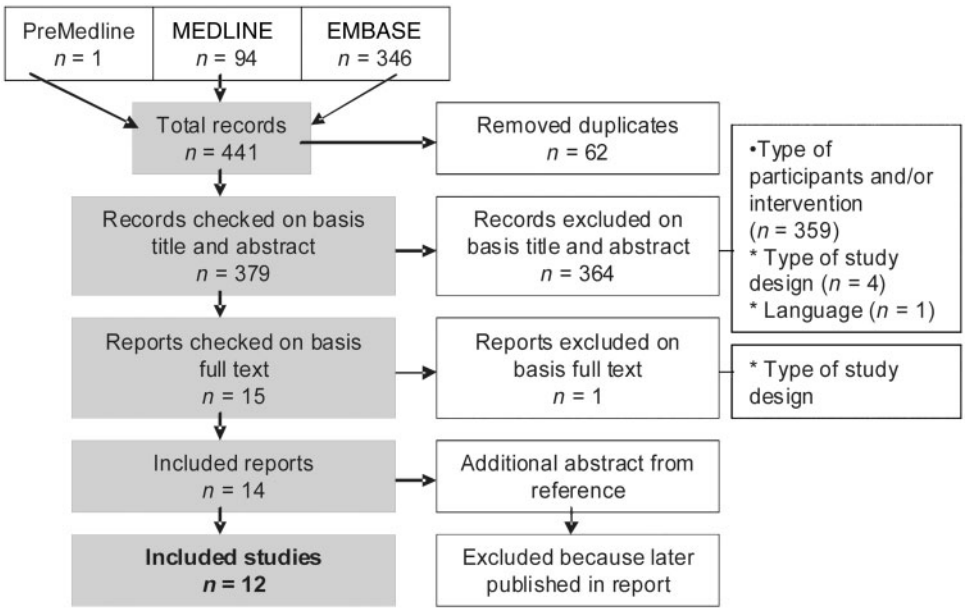
A data extraction sheet was developed. To avoid double counting, data from multiple reports of the same study were merged. Information was extracted from each included study on (i) number of participants; (ii) characteristics of participants (including diagnosis, age, gender, stage of disease, inclusion and exclusion criteria); (iii) type of intervention (including type, location, intensity, frequency, session duration and duration of the exercise training programme, and whether the exercise training programme was in combination with additional experimental treatment); (iv) type of outcome measure (including disease activity, pain, muscle strength, aerobic fitness, functional performance, functional capacity, health status, muscle characteristics, disease impact and fatigue measures (lung function measures were added after the collection process started); (v) type of study design; (vi) report characteristics (including publication date and publication status); and (vii) geographical origin.

For each study that measured muscle strength, the percentage change in group mean muscle strength score was determined for each muscle function tested in that study. The median and range of changes in the group mean of all muscle functions tested in a specific study were determined. It was also determined whether one or more of these muscle functions changed significantly. Furthermore, it was determined whether significant differences after the training period were reported between two groups in one or more muscle functions tested. From the other outcome measures, the baseline mean or median value of a specific measurement tool and the percentage change in group mean or median in this value was determined for each study. It was also determined whether this change was significant. Furthermore, it was determined whether significant differences after the training period between two groups were reported.

Risk of bias within studies

To ascertain the risk of bias in the included studies, two reviewers independently completed the effective public health practice project quality assessment tool [14] in an unblinded manner. This tool is able to deal with any study design and was shown to be suitable for use in a systematic review [15]. It criticizes (i) selection bias, (ii) allocation bias, (iii) confounders, (iv) blinding, (v) data collection methods, (vi) withdrawals and drop-outs, (vii) analysis

FIG. 1 A summary of the study selection process.



and (viii) intervention integrity. The first six components were rated as strong (+), moderate (o), weak (−) or not applicable (NA) in order to provide a global quality rating. Discrepancy between the two reviewers with respect to the component ratings was resolved by consensus. These assessments were not meant for excluding studies from the review or analysis, but for criticizing the risk of bias in the included studies.

Risk of bias across studies

Selective reporting bias was considered by comparison of the outcomes listed in the methods section of the published report with those for which results were presented.

Results

Study selection

A total of 12 studies were identified for inclusion in the review. These studies were described in 14 reports. A detailed explanation of the study selection results is reported in supplementary section 2 (Results), available as supplementary data at *Rheumatology* Online. A summary of the study selection results is depicted in Fig. 1.

Study characteristics

Report characteristics, study design information and participant characteristics of each study are reported in Table 1. Seven studies examined both patients with PM and patients with DM, four studies examined only patients with IBM and one study examined all three patient groups. Disease stages studied were recent onset, active stable and inactive stable. No studies in children were found. Only four studies reported both inclusion and exclusion criteria. One study reported only inclusion criteria and another study reported only exclusion criteria. Intervention characteristics of each study are reported in Table 2. Tables 3–5 describe the different measurement tools that were used by the different studies to examine disease activity and pain (Table 3), muscle strength (Table 4), aerobic fitness, functional performance, functional capacity, health status, lung function, muscle characteristics, disease impact and fatigue (Table 5). As can be seen in these tables, a large variety of measurement tools was used. In the 'Changes in outcome measures' section, the measurement tools and results are described in more detail.

Risk of bias within studies

The quality assessment scores are presented in Table 6. In the randomized controlled trials, no confounders at baseline were present. In the non-randomized controlled clinical trial, baseline values for activities of daily living differed significantly between the training group and the control group; the training group had a higher baseline score compared with the control group. For the other studies, this component was not applicable.

Six studies reported that the outcome assessors were blinded to the intervention or exposure status of the participant. The other studies did not report about blinding. There was only one study [25] that did sample size calculations. All studies used appropriate statistical methods for analysis and performed the analysis by intervention allocation status rather than the actual intervention received.

The percentage of the participants who received the allocated intervention of interest was >80% in seven out of eight studies that reported about this item. One study reported a percentage >60%. Six studies

Table 1 Report, study design and participant characteristics

Authors	Geographical origin	Study design	Group	Study subjects	Male : female	Age, mean ($\bar{x}$) (s.d.) median ($\tilde{x}$) (range)	Disease stage
Spector *et al*. [16]	USA	UT	–	5 IBM	1 : 4	$\bar{x}$ = 66 (50–74)	NR
Wiesinger *et al*. [17]	Austria	RCT	TG	5 PM/9 DM	5 : 9	$\bar{x}$ = 56 (44–68)	Active stable
			CG			$\bar{x}$ = 40 (24–70)	
Wiesinger *et al*. [18]	Austria	NCT	TG	2 PM/6 DM	5 : 3	$\bar{x}$ = 47 (14) (25–64)	Active stable
			CG	5 (PM/DM)	0 : 5	$\bar{x}$ = 50 (18) (27–70)	
Alexanderson *et al*. [19]; Dastmalchi *et al*. [20]	Sweden	UT	–	5;4 PM/5 DM	2;1 : 8	$\tilde{x}$ = 53;54 (27;37–60)	Inactive stable
Alexanderson *et al*. [21]	Sweden	UT	–	7 PM/4 DM	3 : 8	$\bar{x}$ = 49 (17) (23–80)	Recent onset
Heikkila *et al*. [22]	Finland	UT	–	15 PM/4 DM/3 IBM	11 : 11	$\bar{x}$ = 54 (14) (28–81)	NR
Varju *et al*. [23]	Hungary	UT	ER	4 PM/6 DM	5 : 16	$\bar{x}$ = 51 (14)	Early recovery
			CS	5 PM/6 DM		$\bar{x}$ = 44 (15)	Chronic stage
Arnardottir *et al*. [24]	Sweden	UT	–	7 IBM	7 : 0	$\bar{x}$ = 60 (13) (45–78)	NR
Chung *et al*. [25]	Sweden, UK	RCT	CG	10 PM/9 DM	3 : 16	$\bar{x}$ = 59	Chronic stage
			PL	12 PM/6 DM	3 : 15	$\bar{x}$ = 50	
Alexanderson *et al*. [26]; Nader *et al*. [27]	Sweden	UT	–	3 PM/5 DM	4 : 4	$\bar{x}$ = 53 (44–61)	Chronic stage
Johnson *et al*. [28]	Australia	UT	–	7 IBM	4 : 3	$\bar{x}$ = 68 (4) (61–73)	NR
Johnson *et al*. [29]	Australia	UT	–	7 IBM	5 : 2	$\bar{x}$ = 67 (6)	NR

UT: uncontrolled trial; NCT: non-randomized controlled trial; RCT: randomized controlled trial; TG: training group; CG: control group; ER: early-recovery group; CS: chronic stage group; CR: creatine monohydrate supplement group; PL: placebo supplement group; NR: not reported.

Table 2 Intervention characteristics of the studies

Authors	Muscle strength	Aerobic fitness	Other intervention types	Location	Intensity	Frequency (/week)	Session duration (min)	Programme duration (weeks)
Spector *et al*. [16]	Yes	No	No	NR	50–70% max	3	75	12
Wiesinger *et al*. [17]	No	Yes	No	Hospital	60% max	2-3	60	6
Wiesinger *et al*. [18]	No	Yes	No	Hospital	60% max	2-3	60	26
Alexanderson *et al*. [19]; Dastmalchi *et al*. [20]	Yes	Yes	Mobility	Home	Moderate	5	30	12
Alexanderson *et al*. [21]	Yes	Yes	Mobility	Home	Moderate	5	30	12
Heikkila *et al*. [22]	Yes	No	Functional, ESHT, PSS	NR	Intensive	NR	NR	3
Varju *et al*. [23]	Yes	No	Stretching, lung	NR	NR	5	40–60	3
Arnardottir *et al*. [24]	Yes	Yes	Mobility	Home	Moderate	5	30	12
Chung *et al*. [25]	Yes	Yes	Mobility, creatine	Home	Moderate	5	30	26
Alexanderson *et al*. [26]; Nader *et al*. [27]	Yes	No	No	Hospital	Intensive	3	55	7
Johnson *et al*. [28]	Yes	No	Functional	Home	Mild (increasing)	7 (2/day)	NR	16
Johnson *et al*. [29]	Yes	Yes	Stretching	Home	A: 80% HR_{max}; MS: increasing	A: 3; MS: 3; S: 7	NR	12

ESHT: education self-care plus home training; PSS: psychological and social support; A: aerobic training programme; MS: muscle strength training programme; S: stretching training programme; NR: not reported.

Table 3 The different measurement tools that were used by the different studies to examine disease activity and pain

Disease activity
Serum levels of creatine kinase (all studies)
Serum levels of aldolase [17, 18]
Serum levels of cytokines [16]
Serum levels of epinephrine [16]
Serum levels of CRP [19, 21, 23]
ESR [19, 21, 23, 25]
MRI inflammation [19, 21]
Multicolour flow cytometry inflammation [16]
Muscle biopsy inflammation [16, 19, 21, 24]
Visual analogue scale of disease activity, patient [26]
Visual analogue scale of disease activity, physician [26]
Extraskeletal muscle activity [26]
Genome-wide mRNA profiles [27]
Tissue fibrosis [27]
Immunohistochemistry [27]
Pain
Visual analogue scale of pain [19, 22, 23]
Short-form McGill pain questionnaire [25]
Borg CR-10 scale [26]

reported whether the consistency of the intervention was measured. This was done in all the studies. The reasons for some discrepancies with respect to the component ratings of the two reviewers were oversight and differences in interpretation of criteria.

Risk of bias across studies

In all reports, the outcomes listed in the 'Materials and methods' section were presented in the 'Results' section as well.

Changes in outcome measures

Disease activity

None of the disease activity measures in any of the studies worsened significantly from baseline to the end of the exercise training programme. In two studies there was even an improvement. Arnardottir *et al.* [24] found a significant decrease in EN-4- and IL-1Ra-positive cells, which indicates a decreased endothelial cell area and decreased inflammatory activity, respectively. Nader *et al*. [27] found a decreased amount of pro-inflammatory and profibrotic mRNA and an increased amount of anti-inflammatory and anti-fibrotic mRNA. Furthermore, tissue fibrosis and extraskeletal muscle activity were both decreased after training [26]. However, there was no significant decrease of inflammatory molecules at the protein level [27].

Pain

In all five studies that examined pain, none of the measures changed significantly from baseline to the end of the training programme.

Muscle strength

Table 4 mentions the median and range of changes in group means of all muscle functions tested with a specific measurement tool in a specific study. It is also reported whether a study reported significant improvement (+) or worsening (−) in one or more muscle functions tested. Furthermore, it is mentioned whether a study reported a significant difference (*) between two groups in one or more muscle functions tested.

Dynamometer isometric muscle strength. Spector *et al*. [16] did not find significant improvements in isometric muscle strength in the three muscle functions tested. In the study of Varju *et al*. [23], all four of the muscle functions tested in the chronic stage group and two in the early recovery group were significantly improved. In both studies of Wiesinger *et al*. [17, 18], the peak isometric torque of the hip flexors/knee extensors improved significantly in the training group. In the control group there was no increase in the study of Wiesinger *et al*. [17], and even a significant decrease was observed in the long-term follow-up study of Wiesinger *et al*. [18].

Handheld myometer isometric muscle strength. In the study of Johnson *et al*. [28], all nine muscle functions that were tested on isometric muscle strength improved significantly. In a recent study, Johnson *et al*. [29] found a significant improvement in four of eight muscle functions that were trained and tested.

Manual muscle test. None of the included studies that used manual muscle strength tests reported significant changes. However, at the end of the training period in the study of Chung *et al*. [25], the creatine monohydrate supplement group scored significantly higher than the placebo supplement group on shoulder abduction and hip flexion as measured by manual muscle testing. The other muscle functions tested did not differ significantly between the two groups at the end of the exercise training period.

Peak isokinetic torque at 120°/s. Maximal voluntary concentric knee extension and flexion at angular velocity of 120°/s was not significantly changed after training in the study of Arnardottir *et al*. [24].

Three repetition maximum. Improvements in three voluntary repetition maximum dynamic muscle strength in the study of Spector *et al*. [16] were significant in three of five training exercises. The mean leg curl dynamic muscle strength improved by 105%.

10–15 repetition maximum. Improvements in 10–15 voluntary repetition maximum dynamic muscle strength in the study of Alexanderson *et al*. [26] were significant in four of five tested muscle groups. The abdominal dynamic muscle strength was improved 442%.

Grip strength. In the study of Alexanderson *et al*. [26], neither maximal grip strength nor mean grip strength during 10 s significantly changed. Dynamometer grip strength improved significantly in the study of Johnson *et al*. [28], but not in the study of Johnson *et al*. [29].

TABLE 4 The different measurement tools that were used by the different studies to examine muscle strength and the median and range of change in group means of the muscle functions tested

Measurement tool	Authors	Group	Change[a]	Significance
Dynamometer isometric muscle strength	Spector *et al.* [16]		19 (10–65)	NS
	Varju *et al*. [23]	ER	21 (7–27)	+
		CS	43 (19–53)	+
	Wiesinger *et al*. [17]*	TG	29	+
		CG	11	NS
	Wiesinger *et al*. [18]	TG	34	+
		CG	−42	−
Handheld myometer isometric muscle strength	Johnson *et al*. [28]		44 (19−142)	+
	Johnson *et al*. [29]		3 (−10 to 40)	+
Manual muscle test	Spector *et al*. [16]		NR	NS
	Arnardottir *et al*. [24]		4	NS
	Chung *et al*. [25]*	CR	2 (−1 to 13)	NR
		PL	0 (−5 to 13)	NR
	Alexanderson *et al*. [26]		4	NS
	Johnson *et al*. [28]		NR	NS
Peak isokinetic torque at 120°/s	Arnardottir *et al*. [24]		NR	NS
Three repetition maximum	Spector *et al*. [16]		40 (22–105)	+
10–15 repetition maximum	Alexanderson *et al*. [26]		44 (8–442)	+
Grip strength	Alexanderson *et al*. [26]		2 (−3 to 8)	NS
	Johnson *et al*. [28]		(4–24)	+
	Johnson *et al*. [29]		−8	NS

[a]Median (range) change (%) in group means of the muscle functions tested. *Reported significant difference between the two groups in one or more muscle functions tested after the training period. TG: training group; CG: control group; ER: early recovery group; CS: chronic stage group; CR: creatine monohydrate supplement group; PL: placebo supplement group; NR: not reported; +: reported significant improvement in one or more muscle functions tested; −: reported significant worsening in one or more muscle functions tested; NS: not significant.

Table 5 mentions the baseline mean or median value and the percentage change for each study that used a specific measurement tool to examine aerobic fitness, functional performance, functional capacity, health status, long function, muscle characteristics, disease impact or fatigue. In this table it is also reported whether a study reported significant improvement (+) or worsening (−). Furthermore, it is mentioned whether a study reported a significant difference (*) or no significant difference (#) between the two groups after the training period. In supplementary section 3, available as supplementary data at *Rheumatology* Online, the measures of functional performance, functional capacity, health status, disease impact and fatigue are defined.

Aerobic fitness

All four studies that examined aerobic fitness found a significantly improved peak oxygen uptake in the training groups. Despite the fact that both training groups in the studies of Wiesinger *et al*. [17, 18] had the same baseline values of peak oxygen uptake, the group that trained 26 weeks increased much more in peak oxygen uptake (27% improvement) compared with the group that followed the same exercise training programme but only for 6 weeks (12% improvement). The control groups in the studies of Wiesinger *et al*. showed no significant change [17] or even a significant worsening [18] in this measure.

Functional performance

Five different measurement tools were used to measure functional performance. Three of six studies that examined functional performance found no significant change. In both studies of Wiesinger *et al*. [17, 18], the training group improved significantly and the control group did not change significantly. In the study of Varju *et al*. [23], significant improvements were seen in both study groups in the score on the HAQ, but not in the score on the functional independence measure.

Functional capacity

Arnardottir *et al*. [24] observed no significant change in the functional index. However, four other studies [19, 21, 22, 25] reported a significant improvement in this measure after training. The score did not differ significantly between the creatine monohydrate supplement group and the placebo group in the study of Chung *et al*. [25] at the end of the training programme. The functional index-2 used by Alexanderson *et al*. [26] showed a significant improvement only in the amount of shoulder flexion repetitions. Johnson *et al*. [28] found significant improvements in the time to

TABLE 5 The different measurement tools that were used by the different studies to examine aerobic fitness, functional performance, functional capacity, health status, lung function, muscle characteristics, disease impact and fatigue and their corresponding baseline values and percentage changes in group means or medians after training

Outcome measure and measurement tool	Authors	Group	Baseline[a]	Change[b]	Significance
Aerobic fitness					
Peak oxygen uptake	Wiesinger *et al*. [17]*	TG	17.4 ml/min/kg	12	+
		CG	16.9 ml/min/kg	−2.6	NS
	Wiesinger *et al*. [18]	TG	17.5 ml/min/kg	27	+
		CG	17.0 ml/min/kg	−12	−
	Nader *et al*. [27]	–	26 ml/min/kg	19	+
	Johnson *et al*. [29]	–	18.7 ml/min/kg	27	+
Oxygen uptake at VAT	Wiesinger *et al*. [18]	TG	9.8 ml/min/kg	14	+
		CG	NR	NR	NS
Resting heart rate	Wiesinger *et al*. [18]	TG	85 beats/min	−7	NS
		CG	NR	NR	NS
Heart rate response	Johnson *et al*. [29]	–	134 beats/min	3	NS
Lactate levels	Johnson *et al*. [29]	–	4 mmol	15	NS
Self-reported RPE	Johnson *et al*. [29]	–	4.6	0	NS
Functional performance					
Barthel index	Spector *et al*. [16]	–	2.2	−4.5	NS
Modified FASQ	Wiesinger *et al*. [17]*	TG	156.6	20.5	+
		CG	142.6	2.9	NS
	Wiesinger *et al*. [18]	TG	175	11	+
		CG	116	−13	NS
FIM	Varju *et al*. [23]	ER	113	6	NS
		CS	125	0	NS
HAQ	Heikkilla *et al*. [22]	–	1.3	−8	NS
	Varju *et al*. [23]	ER	1.17	−22	+
		CS	1.04	−16	+
	Alexanderson *et al*. [26]	–	0.68	−1	NS
Myositis activity profile	Alexanderson *et al*. [26]	–	MC	MC	NS
Functional capacity					
Functional index	Alexanderson *et al*. [19]	–	48.0	19	+
	Alexanderson *et al*. [21]	–	50.5	14	+
	Heikkilla *et al*. [22]	–	43.9	9	+
	Arnardottir *et al*. [24]	–	35.7	2	NS
	Chung *et al*. [25]#	CR	50.3	13	+
		PL	46.3	12	+
Functional index-2	Alexanderson *et al*. [26]	–	MC	MC	+
AFPT	Chung *et al*. [25]*	CR	31 s	−13	+
		PL	30 s	−7	NS
Time to walk 30 m	Johnson *et al*. [28]	–	41 s	−17	+
	Johnson *et al*. [29]	–	43 s	−31	NS
Step count on 30-m walk	Johnson *et al*. [28]	–	59 paces	−7	NS
	Johnson *et al*. [29]	–	67 paces	−21	NS
Time to climb one stair	Johnson *et al*. [28]	–	14 s	−21	+
	Johnson *et al*. [29]	–	19 s	−20	NS
Max. sit-to-stands	Johnson *et al*. [28]	–	NR	NR	NS
Seven-minute walking distance	Alexanderson *et al*. [19]	–	312 m	30	+
Health status			–		
Short form-36	Alexanderson *et al*. [19]	–	MC	MC	+
	Alexanderson *et al*. [21]	–	MC	MC	+
NHP	Chung *et al*. [25]#	Both	NR	NR	NS
Lung function					
FVC	Varju *et al*. [23]	ER	2.9 l	17	+
		CS	3.5 l	3	NS
FEV_1/FVC	Varju *et al*. [23]	ER	78%	−3	NS
		CS	81%	3	NS
$FEF_{(25-75\%)}$	Varju *et al*. [23]	ER	2.7 l/s	0	NS
		CS	3.4 l/s	6	NS

(continued)

TABLE 5 Continued

Outcome measure and measurement tool	Authors	Group	Baseline[a]	Change[b]	Significance
Muscle characteristics					
MRI whole muscle CSA	Spector *et al*. [16]	–	NR	NR	NS
Muscle biopsy CSA type I	Arnardottir *et al*. [24]	–	4730 μm^2	17	+
	Dastmalchi *et al*. [20]	–	4570 μm^2	8	NS
Muscle biopsy CSA type II	Arnardottir *et al*. [24]	–	3793 μm^2	4	NS
	Dastmalchi *et al*. [20]	–	3658 μm^2	25	+
Muscle biopsy r.p. type I	Arnardottir *et al*. [24]	–	41%	−3	NS
	Dastmalchi *et al*. [20]	–	32%	31	+
Muscle biopsy r.p. type IIA	Arnardottir *et al*. [24]	–	20%	−3	NS
	Dastmalchi *et al*. [20]	–	39%	−13	NS
Muscle biopsy r.p. type IIB	Arnardottir *et al*. [24]	–	31%	−18	NS
	Dastmalchi *et al*. [20]	–	26%	0	NS
Muscle biopsy r.p. type IIC	Arnardottir *et al*. [24]	–	8%	88	NS
	Dastmalchi *et al*. [20]	–	3%	−67	+
Regeneration markers	Dastmalchi *et al*. [20]	–	MC	MC	+
Cap. diam. muscle biopsy	Arnardottir *et al*. [24]	–	90 μm^2	NR	NS
^{31}P MRS PCr/β-NTP	Chung *et al*. [25]	CR	4.83	3	+
		PL	4.03	0.5	NS
^{31}P MRS Pi/β-NTP	Chung *et al*. [25]	Both	NR	NR	NS
Energy metabolism mRNA[c]	Nader *et al*. [27]	–	MC	MC	+
Disease impact					
SGDI	Alexanderson *et al*. [21]	–	3	−33	NS
VAS disease impact	Alexanderson *et al*. [26]	–	2.9	14	NS
HADS	Chung *et al*. [25][#]	Both	NR	NR	NS
Fatigue					
Fatigue severity scale	Spector *et al*. [16]	–	5.5	−5	NS
VAS fatigue	Varju *et al*. [23]	ER	66	−17	+
		CS	51	−61	+
Chalder fatigue score	Chung *et al*. [25][#]	CR	NR	NR	NS
		PL	NR	NR	NS

[a]Group mean or median. [b]Change (%) in group mean or median after training compared with baseline. [c]mRNA related to lipid biosynthesis and oxidative metabolism. *Reported significant difference between the two groups after the training period. [#]Reported no significant difference between the two groups after the training period. +: reported significant improvement in one or more components; −: reported significant worsening in one or more components; NS: not significant; TG: training group; CG: control group; ER: early recovery group; CS: chronic stage group; CR: creatine monohydrate supplement group; PL: placebo supplement group; NR: not reported; MC: multiple components; VAT: ventilatory anaerobic threshold; RPE: rate of perceived exertion; FASQ: functional assessment screening questionnaire; FIM: functional independence measure; HAQ: health assessment questionnaire; AFPT: aggregate functional performance time; Max.: maximum; Min.: minutes; NHP: Nottingham health profile; FVC: forced vital capacity; $FEF_{(25-75\%)}$: forced expiratory flow; FEV_1/FVC: forced expiratory volume 1 s to FVC ratio; MRI: magnetic resonance spectroscopy; CSA: cross-sectional area; r.p.: relative proportion; Cap. diam.: capillary diameter; ^{31}P MRS: ^{31}P magnetic resonance spectroscopy; PCr: phosphocreatine; NTP: nucleoside triphosphate; SGDI: subjective global disease impact; VAS: visual analogue scale; HADS: hospital anxiety and depression scale.

walk 30 m and the time to climb one stair. However, these improvements were not found in a later study of Johnson *et al*. [29]. Alexanderson *et al*. [19] observed a significant increase in the 7-min walking distance.

Health status

Physical functioning as assessed by one component of the short form-36 was significantly improved in the studies of Alexanderson *et al*. [19, 21]. The component role-physical was only significantly improved in the study of Alexanderson *et al*. [19]. Bodily pain and vitality were only significantly improved in the study of Alexanderson *et al*. [21]. The other components of the short form-36 did not significantly change in either study. Chung *et al*. [25] found no significant change in health status as assessed by the Nottingham health profile in both study groups.

Lung function

Only one study examined lung function [23]. The only measure that improved significantly was the forced vital capacity in the early recovery group.

Muscle characteristics

Different methods were used to examine muscle characteristics. Some muscle biopsy cross-section areas and relative proportions of fibre types changed significantly in the studies of Arnardottir *et al*. [24] and Dastmalchi

TABLE 6 The scores of each study on the first six components of the effective public health practice project quality assessment tool [14]

Authors	Selection bias	Allocation bias	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs
Spector *et al*. [16]	–	–	NA	+	+	+
Wiesinger *et al*. [17]	–	+	+	+	+	+
Wiesinger *et al*. [18]	–	O	–	+	+	+
Alexanderson *et al*. [19]; Dastmalchi *et al*. [20]	–	–	NA	+	+	O
Alexanderson *et al*. [21]	O	–	NA	–	+	+
Heikkilla *et al*. [22]	–	–	NA	–	+	+
Varju *et al*. [23]	–	–	NA	–	+	+
Arnardottir *et al*. [24]	–	–	NA	–	+	+
Chung *et al*. [25]	O	+	+	+	+	O
Alexanderson *et al*. [26]; Nader *et al*. [27]	–	–	NA	+	+	+
Johnson *et al*. [28]	–	–	NA	–	+	+
Johnson *et al*. [29]	–	–	NA	–	+	+

The specific scoring criteria can be found in reference [14]. (–): weak; (O): moderate; (+): strong; NA: not applicable.

et al. [20]. Of the three markers of regeneration used in the study of Dastmalchi *et al*. [20] (CD56, vimentin and neonatal myosin heavy chain), only the percentage of vimentin-positive fibres was higher after the training programme compared with baseline. No change in mean capillary diameter was observed in the study of Arnardottir *et al*. [24]. Chung *et al*. [25] examined muscle bioenergetics and found that the ratio of phosphocreatine/nucleotide triphosphates was significantly increased after training in the group that received creatine monohydrate supplements, but not in the control group. Nader *et al*. [27] observed a decreased level of lipid biosynthesis mRNA and an increased amount of oxidative metabolism mRNA after training.

Disease impact

None of the three studies that measured disease impact found a significant change in this outcome measure.

Fatigue

Two out of three studies that examined fatigue found no significant change in this outcome measure. However, the score on the visual analogue scale in the study of Varju *et al*. [23] improved significantly in both study groups.

Discussion

The objective of this systematic review was to examine whether exercise training is safe and effective in patients with an IIM. For this purpose, all experimental studies that assessed the safety and/or efficacy of an exercise training programme in this type of patients were reviewed.

Safety

Exercise training in patients with an IIM appears to be safe since disease activity and pain measures as used in the included studies worsened in none of the studies on a group level. Some studies even reported an improvement in disease activity measures [24, 26, 27].

Some studies reported at an individual level increased creatine phosphokinase levels [22, 25, 26], ESRs [25], muscle fibre pathology [24] and pain [22]. In most of these cases, the values remained within the normal range or the increment was small ($\leqslant$22%). The increased muscle fibre pathology observed in two patients in the study of Arnardottir *et al*. [24] could be due to the fact that the muscle fibre abnormalities have a patchy distribution in IBM. Also, in a few studies, patients stopped the exercise training programme early or the programme had to be adjusted. Reasons for stopping were considered either as related to the exercise training programme or related to other diseases such as osteoporosis and arthritis. None of the studies reported increments in the immunosuppressive treatment during the exercise training programme. In some cases, drug treatment was even reduced due to clinical improvement [19, 21].

It is important to realize that many the studies included examined very specific patient groups, which were expected to be at low risk of disease exacerbation. Patients with other serious medical illnesses and/or patients that are unable to exercise sufficiently to participate were excluded in most of the articles. All articles that described inclusion criteria required that drug therapy was stable for at least 3 months before the start of the exercise programme. Unfortunately, not all studies reported inclusion and exclusion criteria.

Efficacy

The efficacy of exercise training in patients with an IIM was assessed with a large variety of outcome measures. For pooling of future studies, the establishment of a core set of outcome measures is strongly advised. It appears

that exercise training is effective on several different outcomes.

Muscle strength

Studies have reported loss of muscle strength over time in patients with IBM [30, 31]. Moreover, Wiesinger *et al.* [18] found a significant decrement in muscle strength after 26 weeks in patients with DM and PM who did not participate in the exercise training programme. It appears that exercise training might prevent this loss in muscle strength or might even improve muscle strength in patients with an IIM, since all but one of the included studies that examined muscle strength showed in one or more muscle functions tested a significant and substantial improvement in muscle strength after exercise training. Spector *et al.* [16] observed the most marked increases in muscle strength in the least weakened muscles. This could be explained by disuse due to weakness and atrophy of the antagonist muscles, and consequently a greater reserve for muscle contraction and force development of the least weakened muscles.

Aerobic fitness

The results strongly indicate that aerobic training provides benefits in aerobic fitness in active as well as inactive stable patients with DM and PM and patients with IBM. A training period of 26 weeks seems to be superior to a training period of 6 weeks.

Functional performance and functional capacity

Functional measures did improve in most of the included studies. Both studies of Wiesinger *et al.* [17, 18] showed the additional value of exercise training over no exercise training on functional performance.

Several studies reported decreased functional measurements at individual level. However, these decrements were small and were not accompanied by significant worsening of the patients' assessment of disease impact on well-being and/or related to other diseases. One study described a patient that showed deterioration in their functional index (FI) score due to pulmonary fibrosis [22]. Another study described a patient with previous arthritis that caused lessening of shoulder mobility and functional measurements and consequently a decreased FI score after training [21].

Lung function

Only one study included respiratory training and measurements. Significant improvements were only observed in the forced vital capacity (FVC) in the early recovery group. This improvement is thought to be due to increased strength of the respiratory muscles, since the other two parameters, which are fairly independent of muscle strength, did not change significantly [23].

Muscle characteristics

Dastmalchi *et al*. [20] showed that patients with DM and PM had a significantly lower relative proportion of Type I fibres and a higher relative proportion of Type IIB and Type IIC fibres compared with healthy control subjects. After exercise training, the relative proportion of Type I fibres was increased, the relative proportion of Type IIC fibres was decreased, and the cross-sectional area of Type II fibres was increased [20]. This means a closer to normal fibre-type composition, which corresponded to clinical improvements in muscle function. In the study of Arnardottir *et al*. [24], only the cross-sectional area of the Type I fibres changed significantly. Possible explanations for the absence of significant changes in other muscle characteristic variables could be the small number of patients ($n = 4$) in which muscle biopsy was done and the low training intensity. Spector *et al*. [16] did not find any change in whole muscle cross-sectional area as measured with MRI. mRNA results of the study of Nader *et al*. [27] indicate that exercise training induces improvements in oxidative metabolism.

Creatine monohydrate supplements

The improvement in functional capacity seen in patients with DM and PM who underwent exercise training combined with creatine monohydrate supplements was associated with increased muscle creatine phosphate levels [25]. The functional improvement in patients that received placebo supplements was smaller and was not accompanied by increases in muscle creatine phosphate levels. Whether patients with IBM experience any benefit from creatine monohydrate supplements has yet to be investigated.

PM/DM *vs* IBM

Patients with PM/DM and patients with IBM differ from each other in the location of muscle involvement and the responsiveness to drug therapy. To show if there is also a difference in response to exercise training, pooled effects for patients with PM/DM and for patients with IBM should be calculated. However, in this review, there were too few studies using the same measurement tools to do this.

Reasons for no observed improvement

An absence of a significant improvement does not necessarily mean that the exercise training programme was not beneficial. It could be that the measurement tool was unable to detect minor changes in the outcome measure or that the measurement tool and the exercise training programme did not correspond to each other. It could also be that the number of patients was too low to draw significant relevant conclusions. Other possible reasons for the absence of improvements are an insufficient intensity, frequency and/or duration of the exercise programme.

Paediatric patients with an IIM

The subjects in the included studies were all $\geqslant 23$ years. Since children show different physiological responses to exercise compared with adults and the pathophysiology of myositis shows differences between children and adults, the conclusions drawn in this review cannot be extrapolated to children [32–35]. Only one report described the effects of exercise training in a patient

with inactive juvenile DM [36]. This child showed improvements in muscle strength, aerobic fitness and muscle function without increments in disease activity. Another study showed that muscle inflammation as measured with MRI, myometry and blood parameters did not increase immediately after or within 60 min of exercise training in patients with active and inactive juvenile DM [37]. These are promising results, arguing for the relevance of exercise training in children with an IIM. More research is needed to confirm the positive effects of exercise training in children with an IIM.

Bias

Most of the included studies have a high risk of selection bias, which could bias the outcomes of the studies. It is reasonable that only the most active subjects, the most motivated subjects and/or the subjects that believe they can benefit from the exercise programme agreed to participate in the study. This was seen in the non-randomized controlled trial of Wiesinger *et al*. [18] in which the patients were asked whether they wanted to participate in an exercise training programme or not. Patients who decided to participate in the exercise training programme had a much higher baseline score for activities of daily living compared with the non-training patients.

Furthermore, most of the included studies have a high risk of allocation bias as well. Only two randomized controlled trials and one non-randomized controlled trial were included. The other studies did not have a control group. Without a control group it is difficult to prove that a certain improvement was attributed to exercise training and not to something else (e.g. drug therapy). Moreover, selective reporting bias could not be ruled out.

Future research

Based on the findings of this review, it is not possible to prefer one exercise training programme over another. It is important that future studies compare different exercise training programmes with no exercise programme in randomized controlled multicentre trials. The studies have to include enough subjects to allow significant conclusions to be drawn. Moreover, appropriate measurement tools corresponding to the intervention and with enough sensitivity have to be used. The establishment of a core set of outcome measures is indicated. To confirm the additional effects of creatine monohydrate supplements on the training effects, more research is necessary. Furthermore, effects of exercise training in children have to be examined.

Conclusions

In conclusion, it appears that exercise training is safe in adult patients with active as well as inactive stable IIMs. Special attention has to be paid to patients with additional diseases such as arthritis or osteoporosis, because those patients are at increased risk of negative effects from the exercise programme. Furthermore, the results of the included studies strongly indicate that exercise training provides benefits in muscle strength, aerobic fitness and functional measurements. A few indications were found for improved fatigue, health status and lung function after exercise training. No indications for improved disease impact were found.

Rheumatology key messages

- Exercise training appears to be safe and effective in adult patients with a stable IIM.
- Randomized controlled multicentre trials comparing different exercise training programmes with no exercise programme should be done.
- Studies examining the effects of exercise training in children should be done.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Greenberg SA. Inflammatory myopathies: evaluation and management. Semin Neurol 2008;28:241–9.

2 Park JH, Vital TL, Ryder NM *et al*. Magnetic resonance imaging and P-31 magnetic resonance spectroscopy provide unique quantitative data useful in the longitudinal management of patients with dermatomyositis. Arthritis Rheum 1994;37:736–46.

3 Park JH, Olsen NJ, King L Jr *et al*. Use of magnetic resonance imaging and P-31 magnetic resonance spectroscopy to detect and quantify muscle dysfunction in the amyopathic and myopathic variants of dermatomyositis. Arthritis Rheum 1995;38:68–77.

4 Cea G, Bendahan D, Manners D *et al*. Reduced oxidative phosphorylation and proton efflux suggest reduced capillary blood supply in skeletal muscle of patients with dermatomyositis and polymyositis: a quantitative 31P-magnetic resonance spectroscopy and MRI study. Brain 2002;125:1635–45.

5 Hollister JR. The untoward effects of steroid treatment on the musculoskeletal system and what to do about them. J Asthma 1992;29:363–8.

6 Lundberg IE. The heart in dermatomyositis and polymyositis. Rheumatology 2006;45(Suppl. 4):iv18–21.

7 Fathi M, Lundberg IE, Tornling G. Pulmonary complications of polymyositis and dermatomyositis. Semin Respir Crit Care Med 2007;28:451–8.

8 Wiesinger GF, Quittan M, Nuhr M *et al*. Aerobic capacity in adult dermatomyositis/polymyositis patients and healthy controls. Arch Phys Med Rehabil 2000;81:1–5.

9 Plotz PH, Dalakas M, Leff RL, Love LA, Miller FW, Cronin ME. Current concepts in the idiopathic inflammatory myopathies: polymyositis, dermatomyositis, and related disorders. Ann Intern Med 1989;111:143–57.

10 Alexanderson H. Exercise effects in patients with adult idiopathic inflammatory myopathies. Curr Opin Rheumatol 2009;21:158–63.

11 de Salles Painelli V, Gualano B, Artioli GG *et al*. The possible role of physical exercise on the treatment of idiopathic inflammatory myopathies. Autoimmun Rev 2009;8:355–9.

12 Bassuk SS, Manson JE. Physical activity and cardiovascular disease prevention in women: a review of the epidemiologic evidence. Nutr Metab Cardiovasc Dis 2010;20:467–73.

13 Shaw I, Shaw BS, Brown GA, Cilliers JF. Concurrent resistance and aerobic training as protection against heart disease. Cardiovasc J Afr 2010;21:196–9.

14 Thomas H. Quality assessement tool for quantitative studies. Effective public health practice project. Toronto: McMaster University, 2003.

15 Deeks JJ, Dinnes J, D'Amico R *et al*. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7:iii–x, 1–173.

16 Spector SA, Lemmer JT, Koffman BM *et al*. Safety and efficacy of strength training in patients with sporadic inclusion body myositis. Muscle Nerve 1997;20:1242–8.

17 Wiesinger GF, Quittan M, Aringer M *et al*. Improvement of physical fitness and muscle strength in polymyositis/dermatomyositis patients by a training programme. Br J Rheumatol 1998;37:196–200.

18 Wiesinger GF, Quittan M, Graninger M *et al*. Benefit of 6 months long-term physical training in polymyositis/dermatomyositis patients. Br J Rheumatol 1998;37:1338–42.

19 Alexanderson H, Stenstrom CH, Lundberg I. Safety of a home exercise programme in patients with polymyositis and dermatomyositis: a pilot study. Rheumatology 1999;38:608–11.

20 Dastmalchi M, Alexanderson H, Loell I *et al*. Effect of physical training on the proportion of slow-twitch type I muscle fibers, a novel nonimmune-mediated mechanism for muscle impairment in polymyositis or dermatomyositis. Arthritis Rheum 2007;57:1303–10.

21 Alexanderson H, Stenstrom CH, Jenner G, Lundberg I. The safety of a resistive home exercise program in patients with recent onset active polymyositis or dermatomyositis. Scand J Rheumatol 2000;29:295–301.

22 Heikkilla S, Viitanen JV, Kautiainen H, Rajamaki T, Mantyvuo P, Harju T. Rehabilitation in myositis. Physiotherapy 2001;87:301–9.

23 Varju C, Petho E, Kutas R, Czirjak L. The effect of physical exercise following acute disease exacerbation in patients with dermato/polymyositis. Clin Rehabil 2003;17:83–7.

24 Arnardottir S, Alexanderson H, Lundberg IE, Borg K. Sporadic inclusion body myositis: pilot study on the effects of a home exercise program on muscle function, histopathology and inflammatory reaction. J Rehabil Med 2003;35:31–5.

25 Chung YL, Alexanderson H, Pipitone N *et al*. Creatine supplements in patients with idiopathic inflammatory myopathies who are clinically weak after conventional pharmacologic treatment: six-month, double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;57:694–702.

26 Alexanderson H, Dastmalchi M, Esbjornsson-Liljedahl M, Opava CH, Lundberg IE. Benefits of intensive resistance training in patients with chronic polymyositis or dermatomyositis. Arthritis Rheum 2007;57:768–77.

27 Nader GA, Dastmalchi M, Alexanderson H *et al*. A longitudinal, integrated, clinical, histological and mRNA profiling study of resistance exercise in myositis. Mol Med 2010;16:455–64.

28 Johnson LG, Edwards DJ, Walters S, Thickbroom GW, Mastaglia FL. The effectiveness of an individualized, home-based functional exercise program for patients with sporadic inclusion body myositis. J Clin Neuromuscular Dis 2007;8:187–94.

29 Johnson LG, Collier KE, Edwards DJ *et al*. Improvement in aerobic capacity after an exercise program in sporadic inclusion body myositis. J Clin Neuromuscul Dis 2009;10:178–84.

30 Lindberg C, Persson LI, Bjorkander J, Oldfors A. Inclusion body myositis: clinical, morphological, physiological and laboratory findings in 18 cases. Acta Neurol Scand 1994;89:123–31.

31 Rose MR, McDermott MP, Thornton CA, Palenski C, Martens WB, Griggs RC. A prospective natural history study of inclusion body myositis: implications for clinical trials. Neurology 2001;57:548–50.

32 Hiketa T, Ohashi M. Juvenile dermatomyositis—statistical observation of 105 patients with dermatomyositis. Nippon Hifuka Gakkai Zasshi 1991;101:825–30.

33 Kovacs SO, Kovacs SC. Dermatomyositis. J Am Acad Dermatol 1998;39:899–920.

34 Nagaraju K, Rider LG, Fan C *et al*. Endothelial cell activation and neovascularization are prominent in dermatomyositis. J Autoimmune Dis 2006;3:2.

35 Wedderburn LR, Li CK. Paediatric idiopathic inflammatory muscle disease. Best Pract Res Clin Rheumatol 2004;18:345–58.

36 Omori C, Prado DM, Gualano B *et al*. Responsiveness to exercise training in juvenile dermatomyositis: a twin study. BMC Musculoskelet Disord 2010;11:270.

37 Maillard SM, Jones R, Owens CM *et al*. Quantitative assessments of the effects of a single exercise session on muscles in juvenile dermatomyositis. Arthritis Rheum 2005;53:558–64.