Therapy of myositis: biological and physical

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Purpose of review
To give an update on reported use and effects of biological and physical therapies in patients with myositis.

Recent findings
The most promising biological treatment in polymyositis, dermatomyositis and juvenile dermatomyositis is B-cell blockade by rituximab. Anti-Jo or anti-Mi-2 antibodies were predictors of response suggesting different molecular pathways in different subsets of myositis. T-cell blockade with abatacept is a new possibility, as is blockade of interleukin-1, interleukin-6 or type I interferon, but controlled studies are needed. Metabolic abnormalities may contribute to muscle impairment, lending support to combine pharmacological therapy with exercise in patients with polymyositis and dermatomyositis. Exercise improved the aerobic milieu in the muscle, along with improved aerobic capacity, and reduced disability. Support is also provided for the safety of exercise in patients with recent-onset polymyositis and dermatomyositis and exercise is well tolerated in patients with juvenile dermatomyositis.

Summary
There is a strong need to develop new therapies in patients with myositis. To achieve this, more knowledge is needed on the molecular pathogenesis. Targeted therapies using biologics or exercise can be employed to achieve an improved understanding of molecular pathways, provided that clinical outcome measures are combined with molecular studies on muscle and blood.

Keywords
biological treatment, dermatomyositis, exercise, pharmacological treatment, polymyositis

INTRODUCTION

The idiopathic inflammatory myopathies are clinically heterogeneous with common symptoms of muscle weakness and fatigue. Subgroups include adult dermatomyositis, polymyositis, inclusion body myositis (IBM), necrotizing myopathy and juvenile dermatomyositis (JDM). Different clinical and histopathological features indicate that different molecular pathogenic mechanisms may predominate in different subsets of myositis. Subgroups could also be based on the pattern of autoantibodies [1]. Response to pharmacological treatment varies that supports the notion on different pathophysiology in different disease subsets.

The pharmacological treatment of dermatomyositis and polymyositis is based on high doses of glucocorticoids over long periods, often in combination with another immune-modulating agent, most often methotrexate or azathioprine. Other immune-modulating therapies used are cyclosporine, tacrolimus, mycophenolate mofetil and high doses of intravenous immunoglobulin. Despite this treatment, most patients experience persisting muscle weakness or a relapse when the medication is tapered. Therefore, there is an unmet need for new therapies. For patients with IBM, conventional immunosuppressive treatment has limited or no effects, suggesting other molecular mechanisms in the disease process. Concerning the immune-mediated necrotizing myopathies, the molecular pathogenesis is unclear and response to immune suppressive treatment varies.

Recently, it has been recognized that pharmacological therapy by itself may not be sufficient to recover muscle strength, endurance and performance in daily life. In this context, a role of physical

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KEY POINTS

- Promising results have been revealed by targeting B cells in patients with polymyositis, dermatomyositis and JDM. Other biological therapies that may be of further interest are those targeting T cells, type I interferon, interleukin-1 or interleukin-6.
- Adding exercise to immunosuppressive treatment in established polymyositis or dermatomyositis leads to improved strength and performance.
- There is increasing evidence for safety of exercise in active polymyositis/dermatomyositis and juvenile dermatomyositis.
- Effects of exercise in IBM and in JDM need to be further investigated.

exercise has gained attention and combining pharmacological treatment with physical exercise has added value [2,3]. In this review, we will discuss the potential role of biological and physical therapy on the basis of their reported effects in patients with myositis, with a focus on literature review over 2013 to 2014.

BIOLOGICAL THERAPY

The use of biological therapies in patients with other inflammatory rheumatic conditions, such as rheumatoid arthritis, has revolutionized patient care. Remarkably, they have not only improved quality of life, but they have actually changed the disease course and may stop tissue destruction. Although the effects of biological therapy in patients with myositis have been less studied, importantly, the response to targeted therapies, such as biologics, may, in addition to providing benefit to the patients, provide new information concerning the role of particular molecular pathways in different subsets of patients.

Anti-tumor necrosis factor

The reasons for using tumor necrosis factor (TNF) blockade as a treatment for patients with inflammatory myopathies are numerous and include the following: expression of TNF in muscle biopsies, genetic associations with increased TNF production and the more severe disease with cutaneous calcinosis in patients with JDM [4]. Previous reports of anti-TNF treatment are conflicting and were summarized by Aggarwal and Oddis [5].

Over the past year, we found two case reports and one case series reporting positive effects of anti-TNF treatment on disease manifestations in patients with myositis [6–8]. In a case series of 14 patients with dermatomyositis and acute interstitial pneumonia, treated with infliximab in an early phase of disease, 10 cases had improved muscle and lung function, although exact data on improvement are missing [6]. In the same study [6], four cases that were treated later in the disease died. A case with systemic sclerosis and myositis with extensive cutaneous calcinosis on fingers and in the pelvic region improved after 41-month treatment with infliximab infusions [7]. The resolution of calcinosis was confirmed by a pelvic computed tomography scan [7]. A woman with antisynthetase syndrome and anti-Jo-1 antibodies, previously resistant to treatment with conventional immunosuppressive drugs, improved in her arthritis during treatment with adalimumab in combination with leflunomide over 4 years [8]. The authors reported stabilized lung function and normalized muscle enzyme during this treatment.

The positive results from treatment with anti-TNF therapy in myositis need to be considered in the context of reports with patients having flared during anti-TNF therapy with a possible activation of the type I interferon system [9,10]. In addition, there have been several reports of new onset of polymyositis or dermatomyositis or antisynthetase syndrome during anti-TNF treatment of other diseases. Twenty such cases are summarized in a report by Brunasso *et al.* [11]. The TNF-blocking agents in this report include infliximab, adalimumab and etanercept. Taken together, we can conclude that there is heterogeneity in response to TNF blockade. Unfortunately, neither do we have a prognostic marker for response nor for predicting who is at risk of having a flare with TNF blockade. Moreover, TNF does not seem to be a key molecule in the pathogenesis of most patients with polymyositis or dermatomyositis. Thus, other therapies need to be sought.

Rituximab: B-cell depletion

The most promising biological therapy so far is rituximab. The rationale for B-cell blockade is the presence of autoantibodies establishing the involvement of B cells in the pathogenesis of myositis. Up to 90% of myositis patients may have autoantibodies even though some specificities have not been identified (our unpublished data), and B cells and plasma cells have been observed in muscle tissue of myositis patients.

The results of a number of case series between 2005 and 2012 constituted the rationale for the 'Rituximab In Myositis' (RIM) trial [5]. Although the primary endpoint was not achieved, 83% of the randomized patients met the definition of

improvement [12▪▪]. In an ad-hoc study [13▪▪], the presence of anti–Jo-1 and anti–Mi-2 autoantibodies was a predictor of response to rituximab in the RIM trial. This confirms that there is a subpopulation of patients with significant antibody component who are more sensitive to B-cell depletion with rituximab.

During the past year, some more case series with beneficial effects of rituximab have been reported in patients with polymyositis, dermatomyositis and antisynthetase syndrome [14,15]. In a review of publications on rituximab treatment in myositis patients until 2012, 80% of patients improved and the drug was well tolerated in the majority of the reported cases [16]. Even though there is a publication bias to be considered, the number of positive reports on the effect of rituximab argue in favor of this treatment despite the failure to achieve significant difference between the two arms in the double-blind randomized controlled trial (RCT), the RIM trial. Possible explanations for the negative results, including trial design, are discussed in an Editorial [17▪]. The RIM trial underscores the necessity to carefully plan the study design and supports enrolling homogeneous patient populations in future trials. The new myositis response criteria that are being developed will also help predict outcomes more accurately.

Anakinra: interleukin-1 blockade

The rationale for using interleukin-1 blockade in patients with myositis is the consistent upregulation of interleukin-1 alpha and interleukin-1 beta in muscle tissue of these patients. Interleukin-1 receptors are expressed on endothelial cells and in muscle fiber membrane in muscle tissue of patients with polymyositis and dermatomyositis. These receptors may allow interleukin-1 to induce upregulation of adhesion molecules. Thus, interleukin-1 may contribute to chronic inflammatory changes in muscle tissue of these patients.

Two case reports suggested beneficial effect of anakinra in patients with polymyositis/dermatomyositis. In an open mechanistic trial, including treatment-resistant patients with polymyositis, dermatomyositis and IBM, clinical improvement according to the International Myositis Assessment & Clinical Studies Group definition was observed in seven out of 15 patients (three polymyositis, three dermatomyositis and one IBM) [18▪▪]. The improvement was confirmed by improved muscle endurance according to the functional index in myositis [18▪▪]. The clinical improvement did not correspond to clearing of inflammatory infiltrates in muscle tissue, in which interleukin-1 expression was still recorded. However, in peripheral blood, a shift from T helper 17 cells to T helper 1 cells was recorded, indicating a systemic effect of anakinra in favor of T helper 1 immune response. In a pilot study [19▪], including four patients with IBM, no effect on muscle strength was recorded after a mean of 7.7 months of treatment with anakinra. These results indicate a role of interleukin-1 in the pathogenesis of subsets of myositis patients. A larger placebo-controlled trial is indicated.

Abatacept T-cell blockade

A rationale to use abatacept, a T-cell-blocking agent in myositis, is the frequent observation of T cells in muscle tissue of myositis patients. Abatacept is a human fusion protein of cytotoxic T lymphocyte antigen 4 and the Fc portion of human immunoglobulin G1 and acts by inhibiting T-cell activation. Three case reports suggest beneficial effects of abatacept on clinical signs and on serum levels of Creatine kinase in patients with myositis; one case with refractory polymyositis, one JDM case with severe ulceration and refractory calcinosis and a third case with necrotizing myopathy and signs of interstitial lung disease and vasculitis [20,21▪,22▪]. These reports suggest that T cells may have a role in subgroups of myositis. A phase II randomized pilot study with abatacept treatment in patients with adult polymyositis and dermatomyositis is ongoing [*A*batacept treatment in polymyositis and dermamyositis (ARTEMIS)] and may give more information on the effects and tolerance, as well as on possible predictors of response.

Tocilizumab: interleukin-6 blockade

Tocilizumab is an antibody-blocking interleukin-6. With the same reasoning as above that T cells are involved in the pathophysiology of myositis, it makes sense to block interleukin-6 as a cytokine that may activate T cells. Interleukin-6 is overexpressed in muscle tissue of patients with myositis and high levels have been detected in sera of myositis patients. Three case reports suggest beneficial effects of treatment with tocilizumab, two patients with polymyositis [23] and recently one patient with refractory overlap syndrome with dermatomyositis, scleroderma and rheumatoid arthritis [24▪].

Sifalimumab: interferon blockade

The rationale for targeting interferon alpha in myositis is the type I interferon gene signature in muscle tissue and peripheral blood in patients with

dermatomyositis and polymyositis, as well as the interferon-inducing capacity of sera with anti-Jo-1 and anti-Ro/anti-La antibodies. A phase 1b RCT with the interferon alpha-blocking antibody sifalimumab demonstrated a moderate suppression of the type 1 interferon signature in peripheral blood and in repeat muscle biopsies [25▪▪]. The effects on interferon protein expression in muscle biopsies were inconclusive. An ad-hoc study [26▪] reported a coordinated suppression of T-cell-related proteins, such as soluble interleukin 2 receptor alpha, TNF receptor 2 and interleukin-18, in serum after neutralization of the type I interferon gene signature with sifalimumab. These preliminary data support a possible role of type I interferons in the pathogenesis of subgroups of myositis and support the need for further investigations.

PHYSICAL THERAPY

Earlier, only a few studies [27–29] had demonstrated beneficial effects of physical therapy in the form of aerobic exercise alone or in combination with resistance training in patients with established myositis.

Aerobic exercise and resistance training

The mechanisms explaining the beneficial effects may be several. An acquired metabolic disturbance that exercise may reverse has been postulated. Bertolucci *et al.* [30▪] reported abnormal blood lactate levels in 20 patients with established polymyositis/dermatomyositis compared with 15 healthy controls at rest and after an incremental submaximal treadmill-walking exercise bout. Four patients were included in an aerobic treadmill-walking program performed 3 days a week for 6 weeks [30▪]. Reduced lactate levels were seen in all, and two patients improved by more than 20% in physical capacity and three in autonomy in life.

An RCT was undertaken with a 12-week endurance exercise program of ergometer biking, along with resistance training of the quadriceps. The exercise group exercised for 1 h for 3 days a week and was compared with a nonexercising control group [31▪▪]. The exercise group improved in VO_2 max, muscle strength, daily activities and quality of life compared with the nonexercising control group. Intramuscular lactate levels after an all-out cycling session investigated by microdialysis were lower, and the cycling time to exhaustion was doubled in the exercise group but was unchanged in the control group. These observations together with increased mitochondria enzyme activities in muscle tissue indicate that exercise can improve the within-muscle aerobic capacity [32▪▪]. A 1-year open extension revealed that only quadriceps strength improvement was sustained whereas all other variables returned to the baseline values, indicating that continuing exercise is necessary to maintain and improve function and health.

Eight patients with JDM in remission but with muscle impairment, ages 16–42 years, completed a home-based 12-week aerobic exercise program [33▪▪]. The program was well tolerated and resulted in improved VO_2 max, reduced exercise heart rate and improved 6-min walking distance without increased serum Creatine kinase (CK) levels. Ten children between 7 and 17 years with chronic and mild JDM improved in VO_2 max, muscle strength and quality of life without increased release of muscle enzymes after a twice a week 12-week aerobic and resistance training program [34].

Reports on effects of exercise in inflammatory, active, recent-onset polymyositis/dermatomyositis are fewer, but some new studies [35–37] suggest their safety. An RCT confirmed safety of resistance training combined with brisk walking performed 5 days a week, introduced about 4 weeks after start of pharmacological therapy [38▪▪]. The control group performed a range of motion program 5 days a week. After 24 weeks both groups had improved muscle function and aerobic capacity, indicating that the exercise program did not have short-term additional value in this phase of disease. There were no signs of increased inflammation by analysis of muscle biopsies or CPK levels. In an open 2-year follow-up, the exercise group was still significantly improved in muscle function and aerobic capacity and seemingly more physically active compared with the control group, indicating that exercise employed early with regular support might enhance physical activity levels in the long term [38▪▪].

Three patients with active polymyositis with persistent muscle weakness and elevated muscle enzymes despite treatment were introduced to strengthening exercise in combination with aerobic treadmill walking [39▪]. Above 20% improvement was achieved in grip strength and aerobic capacity in one patient, and two improved in daily activities and quality of life. A case report described safety of a 4-week hospital-based rehabilitation program in a young woman with active polymyositis [40].

Resistance training

Safety and efficacy of resistance training have been established by several studies [36,41–46]. Exercise with resistance putty to improve grip strength was feasible and well tolerated in a pilot study [47▪] of patients with established polymyositis/dermatomyositis, but more studies are needed to optimize

Table 1. Exercise studies in adults and children with IIM published 2012–2014

Study/design	Patients/ healthy (*n*)	Diagnosis	Disease activity	Exercise/ duration/ frequency	Load/int. % of max/VRM	Outcome benefits	Results benefits Compared with controls when applicable/ responders (*n*)	Outcome safety	Results safety Compared with controls when applicable/ responders (*n*)
Bertolucci *et al.* 2014 [30▪]	20 patients	PM/DM	Establ.	Aerobic/	60–75%/pred maximal heart rate	Lactate	+ (reduced)	NA	
Controlled/open	15 HC			12 weeks/		6 MWT	0 resp. (*n*)		
	4/20 exercised			3 day/weeks		10 MWT	0		
						TUG	2		
						Autonomy in life	4		
Alemo Munters *et al.* 2013 [31▪▪]	23	PM/DM	Establ.	Aerobic, endurance/	70%/VO_2 max,	VO_2 max	+	6 item	+/EG: resp.
RCT, 1-year open extension				12 weeks/	1 ×30–40 VRM	5 VRM	+	Core set,	$n = 7$ of 11,
				3 day/weeks		MACTAR	+		Resp. n=0
						MAP	+		CG ($p < 0.01$)
						SF-36	+	Biopsies	0
Alemo Munters *et al.* 2013b [32▪▪]	23 patients	PM/DM	Establ.	Aerobic, endurance/	70%/VO_2 max,	Lactate	+ (reduced)	NA	
RCT	12 HC			12 weeks/	1 ×30–40 VRM	Biking time to exhaustion			
(same exercise protocol as [31▪▪])				3 day/weeks		CS	+		
						?-HAD	+		
							+		
Riisager *et al.* 2013 [33▪▪]	8	JDM	Establ.	Aerobic/	65%/VO_2 max	VO_2 max	+	CPK	0
Open study				12 weeks/		6 MWT	+		
				3–4 day/weeks		MMT	0		
						CMAS	0		
Omori *et al.* 2012 [34]	10	JDM	Establ.	Resistance,	3 ×8–12 VRM,	CMAS	+	DAS 28	+
Open study				Aerobic/	70%/VO_2 peak	MMT	+	CPK	0
				12 weeks/		Pat QoL	+		
				2 day/weeks		Par QoL	+		

Alexanderson *et al.* 2014 [38▪▪]	19	PM/DM	Active	Resistance,	NR,	Functional Index,		CPK	0
RCT, 2-years open extension				Aerobic/	50–70%/pred maximal heart rate	VO_2,	0	Biopsy	0
				24 weeks		NHP	0		
				5 day/weeks			0		
Mattar *et al.* 2014 [39▪]	3	PM	Active	Resistance,	3 ×8–12 VRM,	Leg press	0 resp. (*n*)	CPK	1 resp. (*n*)
Case report				Aerobic/	10% blow resp. comp point	Bench press	0	Ald	0
				12 weeks/		Grip	1		
				2 day/weeks		TST	0		
						TUG	0		
						Time to exhaustion	1		
						Time to VAT	1		
						HAQ	2		
						SF-36	2		
Hejazi *et al.* 2012 [40]	1	PM	Active	Resistance (act/pass),	NR	MMT	0, Higher scores	ESR, CRP, CK, AST, ALT	0, Lower values
Case report				Aerobic, ADL/4 weeks/ 5 day/weeks		Hospitalization	Discharged		

ADL, activities of daily living; Ald, ALT, alanine aminotransferase; Aldolase; AST, aspartate aminotransferase; β-HAD, β-hydroxyacyl-CoA dehydrogenase; CG, control group; CK, creatine kinase; CMAS, childhood myositis assessment scale; CRP, C-reactive protein; CS, citrate synthase; DAS, disease activity score; DM, dermatomyositis; ESR, erythrocyte sedimentation rate; Establ., established (chronic) disease; HC, healthy controls; HAQ, health assessment questionnaire; JDM, juvenile dermatomyositis; MACTAR, McMaster Toronto arthritis patient preference questionnaire semi structured interview; MAP, myositis activities profile (activities of daily living); MMT, manual muscle test; MWT, minute walking test; NA, not available; NR, not registered; NHP, Nottingham health profile; PM, polymyositis; Par QoL, Parents PedsQL; Pat QoL, Patients PedsQL; PM, polymyositis; RCT, randomized controlled trial; Resp. (*n*), number of responders, that is improving more than 20% compared with the baseline; SF-36, SF 36 short form (quality of life); TST, timed stands test; TUG, timed-up and go test; VAT, ventilator anaerobic threshold; VO_2, oxygen uptake; VRM, voluntary repetition maximum; 1 ×30–40 VRM, 30–40 VRM performed in 1 set; 3 ×8–12 VRM, 8–12 VRM performed in 3 sets.

the training program. Available studies [48–50] support safety of resistance training in IBM, but results regarding efficacy to improve function are inconclusive and more studies are needed. All exercise studies published within the annual period of review are presented in Table 1.

Recommendations for exercise

Patients with recent-onset polymyositis/dermatomyositis could be introduced to resistance training in combination with aerobic exercise about 4 weeks after starting medical treatment or as soon as they can cope with exercise. The exercise intensity needs to be adapted to individual levels of muscle impairment, fatigue and disease activity. Muscle strength and disease activity should be monitored regularly and exercise load and intensity should be adapted according to the clinical improvement. In patients with low disease activity, exercise could be performed on 65–70% of maximal oxygen uptake or maximal heart rate, 2–3 days a week. To improve muscle strength, strength training should be performed on loads of 10 Voluntary repetition maximum (VRM) (ca 70% of 1 VRM), 2–3 days a week. On the basis of the small number of studies evaluating exercise effects in JDM and IBM, it is too early to make recommendations for these patients.

CONCLUSION

Careful clinical, serological and histopathological characterization will be important in future clinical trials with biologics to identify prognostic markers for response and to achieve a better understanding on the molecular mechanisms that are important in different subgroups of myositis. Recent studies have strengthened the scientific evidence supporting exercise as an important part of the treatment in polymyositis and dermatomyositis and have contributed to our understanding of mechanisms for muscle weakness and exercise response. Recent studies have started to form evidence, supporting efficacy of exercise also in JDM.

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Conflicts of interest

For Ingrid E. Lundberg: Novartis, Servier, Bristol-Myers Squibb and Astra Zeneca.
For Jiri Vencovsky: Novartis, Servier and Bristol-Myers Squibb.

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