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Review

Treatment and investigation of idiopathic inflammatory myopathies

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The idiopathic inflammatory myopathies (IIM) are systemic connective tissue diseases which are characterized by symmetrical, proximal muscle weakness, decreased muscle endurance and chronic inflammation in muscle tissue [1–3]. They can be subclassified into dermatomyositis, polymyositis and inclusion body myositis (IBM) according to differences in clinical as well as histopathological features [1, 4]. Dermatomyositis may occur in both adults and children; in this review, we will, however, focus on the treatment of adult forms of myositis only. Myositis may exist as a disease entity on its own or may be linked to another inflammatory connective tissue disease such as systemic sclerosis or mixed connective tissue disease. Myositis may also be associated with a malignancy, this is particularly true for dermatomyositis, but the association with polymyositis is more controversial [1]. The IIM are chronic disorders in most cases and up to two-thirds of patients develop residual functional impairment [5–7]. Several immunosuppressive treatments are available for inflammatory myopathies, yet for many patients recovery is incomplete [5, 8]. Life-long immunosuppressive therapy is often required, adverse side-effects are common and more effective therapies with fewer side-effects are needed [9]. During the last few years, publications of treatments have been dominated by a number of comprehensive review articles, but very few new therapeutic trials have been reported [8, 10–15]. This review will discuss the currently recommended treatment modalities in adult IIM and summarize recently published therapeutic studies mainly focused on cyclosporin A, i.v. immunoglobulin (IVIg) and on non-pharmacological treatment through physical exercise. We also wanted to focus on investigations that could be performed to assess the effect of treatment, and finally to discuss the possibilities of new treatments based on current knowledge of molecular mechanisms believed to be of importance in these disorders [16, 17].

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The pathophysiological basis for treatment of IIM

The primary aim for treatment of myositis is to improve muscle function. The molecular background of muscle weakness in myositis is currently largely unknown. There is a lack of correlation between the extent of muscle weakness and degree of muscle inflammation as assessed by the presence of inflammatory cell infiltrates in muscle tissue or serum levels of muscle enzymes [18, 19]. In some cases, there is no detectable infiltrate of inflammatory cells despite muscle weakness and this is particularly common in dermatomyositis and IBM [20, 21]. Furthermore, patients with polymyositis and dermatomyositis often continue to exhibit reduced muscle strength, even after intense immunosuppressive treatment and subsequent disappearance of inflammatory infiltrates [18, 22]. Efforts to date have also been unsuccessful in the identification of other morphological changes, such as muscle atrophy or replacement of muscle tissue by fat, which may be responsible for persistent muscle weakness [22]. Based on these observations, it is likely that factors other than the inflammatory process *per se* are involved in the mechanisms causing muscle weakness. This hypothesis is further supported by metabolic abnormalities such as reduced levels of phosphocreatine (PCr) and adenosine triphosphate (ATP), as detected by magnetic resonance spectroscopy (MRS), indicating defective energy metabolism in both dermatomyositis and polymyositis cases [23–25].

From the preceding discussion, it is clear that a better understanding of basic pathophysiological mechanisms is needed in order to improve the treatment of these conditions. One way of contributing to such knowledge is obviously to include pathophysiologically directed investigations in longitudinal clinical studies of myositis. Such investigations should include standardized assessments of muscle function, including measurements of

muscle strength and endurance, as well as molecular studies on repeated muscle biopsies and repeated MRS investigations. Very few studies have actually assessed the effect of a given therapy on muscle inflammation by investigating the histology of repeated muscle biopsies and correlated these findings to muscle function [18, 26]. Thus, the molecular effect on muscle inflammation of most immunosuppressive drugs used today is largely unknown. Until such studies have been undertaken, we can only adhere to the currently recommended treatments for IIM, which are largely based on uncontrolled studies with assessment of clinical and/or biochemical outcome. Furthermore, these studies are limited by the fact that several different tests of muscle function and strength have been used, which makes comparisons of the outcome between different studies problematic [5, 26–30].

Pharmacological therapy

Corticosteroids

The general recommended treatment of IIM consists of corticosteroids in high doses for the initial few months, with or without other immunosuppressive therapies [1, 8, 11, 15]. Placebo-controlled trials of corticosteroid treatment have never been performed and the optimal initial dosage of corticosteroids, as well as duration of treatment, is therefore uncertain. The only prospective study of corticosteroids found in a literature survey was one in which the effect of prednisone alone was compared to the effect of prednisone together with azathioprine. Eight patients with polymyositis received 60 mg/day of prednisone as a starting dose and six out of eight acquired improved muscle function after 3 yr, although none recovered normal muscle function [31].

In retrospective studies, improved muscle function was observed with an initial dose corresponding to prednisone 40–60 mg/day in 60–80% of the patients assessed by the manual muscle test (MMT) or by one of several muscle function scales [5, 27–29, 32, 33]. It is noteworthy that although a majority of patients improved, a complete recovery rate was reported in only 24–43%. The duration of the high prednisone dose ($\geqslant$40 mg/day) in these studies varied between 4 days and 9 weeks [5, 20, 28, 33]. In the retrospective study of Henriksson and Sandstedt [5], a significant correlation was determined between the degree of functional improvement using a four-graded score and a mean total dose of at least 0.5 mg/kg/day during the first 3 months compared to 0.3 mg/kg/day. In a more recent retrospective study, a clinical response rate of 86% was recorded after an initial dose of $\geqslant$0.75 mg/kg/day [30]. In two other retrospective studies, a spontaneous response rate of 50% was reported [34, 35], while in another small study the spontaneous response rate was 0 [27]. In retrospective studies in which survival rate was used as an outcome measure, no difference was evident between low-dose ($<$10 mg/day) and high-dose ($\geqslant$20 mg/day) corticosteroids [36], or between treated and untreated myositis patients [35, 37], even though a higher mortality rate was reported in myositis before the corticosteroid era [38, 39]. These discrepancies in outcome mainly emphasize the limitation of retrospective studies, in which patient groups are not always well defined, and treatment and assessment methods are not standardized.

Given the fact that no placebo-controlled trials with the use of corticosteroids have been performed, our interpretation of existing data is that a starting dose of prednisone of 0.75 mg/kg/day (which corresponds to 40–60 mg/day) is likely to suffice in most myositis patients. No data on outcome have been published to support the often recommended dose of 1–2 mg/kg/day (or 80–100 mg/day) for 4–12 weeks [1, 3, 8, 10] as favourable compared to doses of 40–60 mg/day. We would also recommend that the initial high dose of corticosteroids is maintained for 4–12 weeks; this recommendation is based on the observation of a maximal improvement after a mean of 12 weeks [5, 29, 40, 41]. Reduction of the corticosteroid dosage should be guided by improved muscle function [1, 2, 15, 27]. We suggest that tapering of corticosteroid dosages should be initially conducted in small decrements of $\sim$20% of the daily dosage per month and that tapering could be started when a normal or close to normal muscle function has been achieved, regardless of persisting elevated creatine phosphokinase (CPK) levels. Corticosteroid treatment in consolidation dosages of 5–15 mg/day is often required for several years. A mean duration of treatment of 3 yr was observed in one study, and although some patients still had relapses upon withdrawal of corticosteroids, a gradual tapering of the corticosteroids to withdrawal should be attempted anyway after 2–3 yr [28].

Other immunosuppressive treatment

Although most patients with poly- and dermatomyositis respond, at least partially, to corticosteroids, $\sim$30% of patients do not respond at all [5]. Moreover, in a long-term follow-up study, a substantial number of patients developed increased disability over time due to side-effects of the corticosteroid treatment [9]. These observations emphasize the need for improved treatment for patients with IIM. Several immunosuppressive agents have been reported both as steroid-sparing agents as well as beneficial in patients who are steroid resistant, but few controlled therapeutic trials have been performed. Azathioprine was reported to have a steroid-sparing effect as well as a favourable effect on clinical function compared to prednisone alone in a placebo-controlled trial [31]. Notably, the effect on muscle function was significant not at the 3 month follow-up of the blind study, but after 1 and 3 yr and when the code had been broken, and the steroid-sparing effect was not significant until after 3 yr [18, 31]. The lack of difference in muscle strength, as measured by MMT, after 3 months is not surprising as the patients were given the same corticosteroid dose during this first part of the study and 3 months is far too short a time to

expect the full effect of the immunosuppressive treatment [5]. It is more remarkable that there was significantly less functional disability after 12 months treatment as assessed by the relatively crude functional disability index and considering the low number of patients in each group. In another placebo-controlled trial, IVIg was beneficial in treatment-resistant dermatomyositis patients both on muscle function and on muscle histopathology [26]. Adding plasmapheresis had no positive effect compared to corticosteroids alone in a third controlled trial [42]. A combination of oral methotrexate with azathioprine may be of benefit to treatment-resistant poly- and dermatomyositis cases according to a recently published controlled trial [43]. However, the study lacked power to compare the two treatment regimens directly, the other treatment being i.v. methotrexate with leucovorin rescue, which may also benefit some patients with refractory myositis [43].

In addition to these controlled trials, open studies and case reports indicate a positive effect of methotrexate on muscle function in steroid-resistant cases [44, 45]. The doses of methotrexate have varied between 7.5 and 25 mg/week administered orally or i.m., or up to 100 mg/week i.v. [44, 45]. In an additional open retrospective study, male myositis patients with Jo-1 antibodies with incomplete clinical response to corticosteroids were reported to have a more favourable clinical response to additional treatment with methotrexate compared to azathioprine [30]. The effect of cyclophosphamide in IIM is more controversial. In one open study, some patients were reported to benefit from daily oral cyclophosphamide [46], even though i.v. pulse cyclophosphamide was reported to be ineffective in another open study [47]. Chlorambucil had a beneficial effect in a few treatment-resistant dermatomyositis cases [48]. During recent years, cyclosporin A has been relatively widely used in juvenile dermatomyositis [49–52]. In adult myositis, there are only a few reports on the beneficial effects of cyclosporin A, mainly in treatment-resistant poly- and dermatomyositis cases (Table 1) [53–57]. Notably, the effect is often evident within a few weeks of treatment. In one open study of adult dermatomyositis, cyclosporin A was reported to be beneficial as a first-line drug without corticosteroids [58].

Finally, in addition to the above-mentioned controlled trial of IVIg in polymyositis and dermatomyositis, a few open studies have been presented. In one such study, IVIg as an initial treatment without corticosteroids was insufficient to suppress disease activity in patients with polymyositis and dermatomyositis [59]. In another open study, IVIg was beneficial on muscle strength, function and muscle enzyme levels in a few treatment-resistant cases with dermatomyositis or polymyositis, but not in patients with IBM [60]. From the studies on IVIg treatment in poly- and dermatomyositis undertaken so far, one can conclude that treatment-resistant cases with dermatomyositis could benefit from IVIg infusions, but further studies are needed to clarify the effect in patients with polymyositis. However, IVIg does not cure patients

TABLE 1. Reports on cyclosporin A in the treatment of adult myositis during the last 5 yr

Reference	Diagnosis	No. of patients	Cyclosprin A dose initial dose	Duration of treatment (months)	Effect	Reported side-effects
Grau *et al.*[a] [58]	DM	10	5–10.0 mg/kg/day	3–24	Improved strength 9/10	1 HT, 1 renal failure
Saadeh *et al.* [53]	JDM/DM	2	2.0 mg/day + IVIg	6, 17	2/2 improved	None
Tellus and Buchanan [55]	PM/ILD	1	200 mg/day	~24	Improved strength + ILD	n.a.
Dawson *et al.* [56]	PM/ILD	1	250 mg/day	24	Improved ILD	Increased s-creatinine
Maeda *et al.* [57]	PM/DM	14	200–250 mg/day	n.a.	9/14 improved	1 aspergillosis, 1 renal imp.

DM, dermatomyositis; JDM, juvenile dermatomyositis; PM, polymyositis; ILD, interstitial lung disease; HT, hypertension; n.a., no available information; renal imp = renal impairment.
[a]Cyclosporin A was used as a first-line drug in this study.

with dermatomyositis as a prolonged time of infusions is required [26].

Treatment of IBM necessitates a separate discussion. This entity was first identified as treatment-resistant polymyositis [61] and was followed by other case reports on myositis patients being refractory to corticosteroid treatment and with a corresponding histopathology [62–64]. Only a few therapeutic trials including IBM patients have been reported on in the literature. In three retrospective studies, ~50% of IBM patients responded to corticosteroids with temporarily or partially improved muscle function, but none recovered completely; some improved on methotrexate, but none had a complete response [30, 65, 66]. In a prospective trial, 2/9 patients improved regarding muscle function after combination therapy with methotrexate and azathioprine, and 4/9 had a stabilization of disease progress [66]. In the same study, i.v. methotrexate (0.5 g/m^2 every 2 weeks) with leucovorin rescue resulted in improved muscle function in 1/10 cases and stabilization of disease progress in 7/10 [66]. In a recently published placebo-controlled study, functionally important improvement of muscle function was observed in 6/19 patients after a 3 month trial with IVIg, but there was no significant difference compared to the placebo group [67]. There were regional effects on certain muscle groups of the lower extremities and muscles controlling swallowing function; however, they were of unknown clinical significance. Half the patients chose to pursue the IVIg therapy because, according to their own assessment, it had made a difference in their daily activities and quality of life [67]. In contrast, muscle strength was found to be worsened in all nine patients given IVIg in an open trial [68]. From these limited numbers of therapeutic trials hitherto performed in IBM, it is still controversial whether immunosuppressive drugs have a beneficial effect in this disease entity; some patients have a temporary or stabilizing effect on clinical symptoms, but so far there are no reports on recovery of muscle function. This therapeutic problem also reflects the fact that the pathophysiology behind the clinical symptoms is even less well known for this subgroup of myositis than for poly- and dermatomyositis, and there is still a debate about whether the inflammatory changes in muscle tissue are primary or secondary phenomena in IBM. Interestingly, persisting inflammation in muscle tissue was observed after a median of 60 months of corticosteroid treatment in one study [69]. On the contrary, in another study, a decreased cell infiltration was observed in muscle tissue after an average of 13.6 months of corticosteroid treatment, but still muscle function deteriorated [70]. These studies emphasize the need for more controlled trials including larger patient groups, as well as the need for investigations on the effects of a given therapy both on muscle function and on the cellular and molecular events in muscle tissue.

Our interpretation of these therapeutic reports in IIM is that immunosuppressive drugs should be included from the start of therapy, as was previously advocated by some authors [8]; the reasons for this being both the high risk of corticosteroid-related side-effects and the risk of non-responsiveness to corticosteroid treatment alone. According to the data mentioned above, azathioprine should be the first choice as a steroid-saving drug. Although methotrexate is often used in clinical practice, the efficacy of this drug in IIM still needs to be evaluated in a controlled trial. The data are less clear regarding the beneficial effect of adding cyclophosphamide, cyclosporin A, IVIg or chlorambucil compared to corticosteroids alone, and more controlled trials are necessary before general therapeutic recommendations can be made.

Non-pharmacological therapy

Despite the pronounced functional deficit in patients with myositis, the non-pharmacological interventions have received little attention. An important but controversial treatment of IIM is physical exercise. Because of fear of causing disease flare-ups, patients with myositis have been recommended to avoid active exercise. Recent studies, however, have demonstrated that active exercise could be safely performed in patients with chronic, stable poly- and dermatomyositis without increased muscle inflammation assessed by CPK [71] or by muscle biopsies and magnetic resonance imaging (MRI) [72], and with beneficial effect on muscle function. Beneficial effect on muscle strength after bicycle and step aerobic training for 6 weeks was reported in patients with chronic, inactive poly- and dermatomyositis in a recently published controlled study of 14 patients [73]. There is one report on exercise in IBM including five patients who gained increased muscle strength after 12 weeks of progressive, resistive exercise without increased disease activity as assessed by CPK levels [74]. The effects of exercise in addition to drug treatment in patients with active, recent-onset disease have only been investigated in a limited number of patients so far, although with beneficial effect on muscle strength and function, and without signs of increased disease activity [75, 76]. Whether active physical exercise should be introduced during the early stage of treatment to diminish the risk of persisting, chronic muscle weakness is still unclear and can only be addressed by a controlled trial. The recommendation today is gradually to include active physical exercise when disease activity begins to regress; this exercise could include a light to moderate home exercise programme or a low-intensity aerobic programme on a cycle or in the pool [72, 77].

Investigations for assessment of treatment

Both for the physician who is going to monitor treatment for individual patients and for the purpose of assessing the effects of therapies in controlled trials, there is a need to measure disease activity and to distinguish disease activity from chronic, irreversible changes that cause disability. Currently used diagnostic tools—muscle biopsy, elevation of serum enzyme activity, such as CPK, and characteristic electromyography features—

have never been validated as follow-up measures and are hampered by various limitations [20, 78–83] (Table 2). The most often used assessments for therapeutic responses are clinical evaluation of muscle strength and serum muscle enzyme activity [5, 27, 29, 84]. Recently, MRI, MRS, muscle ultrasound and anti-myosin scintigraphy have been introduced as possible tools for both diagnostic purposes and for assessment of disease activity [24, 85–92]. Although there is a general agreement that muscle function is the most relevant factor for evaluating therapeutic responses, there is no consensus as to how this should be assessed. Moreover, as a reduction of muscle function could be the result of both active muscle inflammation and chronic fibrotic changes, the measurement of muscle function needs to be combined with one or several tools that could reflect active muscle inflammation. Thus, there is a strong need for a standardized outcome measurement which reflects disease activity; such an activity index is currently being developed for juvenile dermatomyositis [93, 94] and it will be important to develop a similar instrument for adults with myositis.

Functional assessment

Muscle weakness is a complex result of decreased strength and endurance which should be recognized when choosing a tool to measure muscle function. Many patients with myositis experience both impaired muscle strength and muscle endurance; however, some patients, particularly those who have partly recovered muscle function during treatment, can often manage a strength test once or twice, but cannot do repeated tests or a longer exercise using the same muscle group. A test which measures muscle endurance is more sensitive and is more likely to detect impaired muscle function than a strength test in this particular group of patients. Furthermore, the muscle tests should measure functions which are relevant to the patients. The most commonly used technique for assessing muscle function is the MMT with the MRC scale [95]. There are several drawbacks to this method: firstly, its sensitivity to changes is low and has not been validated in follow-up studies; second, definition of improvement has never been agreed upon or validated; finally, it requires patient cooperation and is time consuming. A more sensitive technique to measure muscle strength is the modified sphygmomanometer, but its use is limited by the high interobserver variation [96]. A better interobserver reliability was observed with the use of a handheld pull-gauge, another tool to measure muscle strength; however, its usefulness in a longitudinal study has not been validated [97]. All these tests measure strength and not endurance; furthermore, the relevance of these tests to the patients has not been validated. An isokinetic dynamometer is a sensitive tool to measure muscle strength as well as endurance, but is generally not available in a rheumatology practice and requires a trained person to conduct the tests. A 'Timed-Stands' test, measuring the time needed to stand 10 times from a standard chair, was reported with good sensitivity to changes, but the major limitation is its confinement to the lower extremities [98]. The Functional Index of Myositis [99] measures endurance and strength, and is feasible to use in a follow-up study of exercise [72]. It requires a physiotherapist to perform the tests, but not any specialized equipment. However, for this test, we also determined a limitation in sensitivity to changes in those cases with a low degree of muscle weakness. Functional tests based on questionnaires have been used, but not validated among patients with IIM, neither have functional disability scales, and there is a lack of agreement upon a definition of improvement in these scales [5, 27, 28]. Thus, the Functional Index of Myositis [99] is by our means the most useful and reliable functional test for clinical practice, but it still requires further validation if it is to be used as a single test in therapeutic studies.

Laboratory investigations

As muscle function alone does not discriminate between active and chronic disease, a combination with laboratory investigations is required. Erythrocyte sedimentation

TABLE 2. Proposed revised criteria for the diagnosis of idiopathic inflammatory myopathies [80][a]

1.	Symmetric[b], proximal muscle weakness
2.	Elevation of the serum levels of enzymes including not only CK levels, but also aldolase, AST, ALT and lactate dehydrogenase levels
3.	Abnormal electromyogram with myopathic motor unit potentials, fibrillations, positive sharp waves and increased insertional irritability
4.	Muscle biopsy features of inflammatory infiltration and either degeneration/regeneration or perifascicular atrophy
5.	Any of one of the myositis-specific autoantibodies (an antisynthetase, anti-Mi-2 or anti-SRP)
6.	Typical skin rash of DM that includes Gottron's sign, Gottron's papules or heliotrope rash

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase.

[a]Possible idiopathic inflammatory myopathy (IIM) = any two criteria; probable IIM = any three criteria; definite IIM = any four criteria. Results of magnetic resonance imaging that are consistent with muscle inflammation may be substituted for either criterion 1 or 2. Patients with IIM who satisfy criterion 6 may be subclassified as having dermatomyositis (DM). Those who satisfy the proposed criteria for inclusion body myositis [6] may be subclassified as having inclusion body myositis. The application of these criteria assumes that known infectious, toxic, metabolic, dystrophic or endocrine myopathies have been excluded by appropriate evaluations. Criteria 1, 2, 3, 4 and 6 are the original Bohan and Peter criteria in similar form.

[b]Symmetry is intended to denote bilateral, but not necessarily equal, involvement.

rate and other acute-phase reactants are only elevated in a limited number of cases with IIM, and are hence not useful in assessment of disease activity [100]. There is also a limitation to the use of muscle enzymes such as CPK as the only measure of disease activity since in some myositis patients with active disease the level of CPK activity was normal [28, 29, 101], and other patients have persistent elevated muscle enzyme without other signs of disease activity and normal muscle function [8]. Previous reports also indicated that serum CPK activity could be in the normal range even when abnormal anatomical and biochemical changes were observed [29], and in therapeutic trials laboratory responses including CPK, aldolase and lactate dehydrogenase (LD) levels were more common than improved muscle function [30]. Serum CPK levels are also influenced by exercise [102, 103]. Other muscle enzymes such as LD and aldolase are less specific indicators of muscle injury than CPK, as both aldolase and LD are present in other organs such as the liver [21]. Thus, in many cases with IIM, serum muscle enzymes may not be a reliable indicator of disease activity and there is a need for additional measurements to assess disease activity.

Muscle biopsy

Muscle histology is the most sensitive way to assess muscle changes, but it may not be an ideal way to monitor the efficacy of therapy with the current most frequently employed technique, the open muscle biopsy, due both to the inconvenience for the patients and the cost. This problem could be overcome by performing percutaneous conchotome muscle biopsies which give a good diagnostic yield and which can be performed with little discomfort for the patients, and which allow for repeated biopsies [104]. This semi-open biopsy technique can easily be performed by the rheumatologist in an out-patient clinic with a very low complication rate, and could be included as a tool for assessment of disease activity in clinical trials [105]. The problem with 'skip lesions' could be reduced by taking several biopsies from the same incision [106]. Another way to overcome this problem is to use MRI to select an appropriate site for muscle to be biopsied [107, 108]. Further knowledge of disease pathogenesis and the effect of treatment at a molecular level could be obtained by performing repeated muscle biopsies and by correlating histological findings to clinical outcome.

Magnetic resonance imaging

MRI can be used to examine anatomical changes in diseased muscle non-invasively and to assess disease activity, but it cannot replace muscle biopsy for diagnostic evaluation. It may be more sensitive and specific than ultrasound for diagnosis of IIM, especially in cases in which muscle enzymes are normal [109]. The sensitivity and specificity of MRI in the diagnosis of myositis are dependent on the technique employed; in muscle of acute polymyositis and dermatomyositis patients, oedema was observed using T2-weighted and/or short tau inversion recovery (STIR) imaging, whereas normal images were found using T1-weighted imaging [87, 110–113]. In chronic polymyositis and dermatomyositis patients, muscular atrophy of variable distribution and fatty infiltration within the atrophied muscles were reported using a combination of T1-weighted and fat-suppressed MRI, and the elevated fatty replacement correlated with the duration of the disease [25, 87, 112, 113, 116–120]. Fat-suppressed imaging is needed to differentiate between fat and oedema, as fat gives rise to hyperintense signals in both T1- and T2-weighted images, and oedema may be masked by concurrent fatty changes.

MRI of muscles is also a feasible non-invasive assessment tool to use for follow-up studies as a strong correlation was determined between increased T2 and STIR signal intensity and muscle function [112, 114] and disease activity [87, 110, 111, 114, 115]. Already published data from therapeutic studies support the usefulness of MRI with T2 and STIR signal intensities of muscle, which returned to normal when there was clinical improvement after therapy [112, 114, 115, 121]. Thus, it is possible that consequent imaging sequences could provide insight into pathogenesis of the myositis. More work is needed, however, to determine the relationship between MRI and clinical parameters such as muscle strength, muscle function, muscle histopathology and the level of serum activity.

Phosphorus magnetic resonance spectroscopy

A number of groups have used MRS to investigate inflammatory muscle disease [23, 24, 113, 122–124]. These studies have primarily focused on phosphorus MRS, which allows assessment of muscle bioenergetic metabolites such as PCr and ATP. In dermatomyositis cases with muscular symptoms, ATP and PCr levels were reduced, while the ratio of inorganic phosphate (Pi) to PCr (Pi/PCr) was increased relative to controls even at rest. These metabolic abnormalities were further accentuated with exercise [23, 24, 113]. In amyopathic dermatomyositis, resting ATP and PCr levels and the Pi/PCr ratio were similar to controls, but during exercise the Pi/PCr ratio was elevated with no significant ATP loss [122, 124]. Interestingly, these studies support the hypothesis that metabolic disturbances are at least partly involved in the pathogenesis of the muscle weakness and endorse the need for alternative therapies to the currently used immunosuppressives. Muscle bioenergetic defects preceded other changes and even persisted after resolution of inflammation [24, 124]. Phosphorus MRS may thus have the potential to be used as a tool to evaluate therapeutic regimens [24, 123, 125].

Proton magnetic resonance spectroscopy

Two studies have reported the use of proton MRS to assess patients with myositis. In a sequential report of a juvenile dermatomyositis case, proton MRS determined an abnormally low lipid-to-water ratio at the onset of the disease and the latter ratio became abnormally high compared to controls at 3 months of treatment [126]. This observation may reflect oedema

formation during onset of the disease, which diminished after treatment (as confirmed by MRI), and lipid deposition in muscle during chronic stages of the disease [126]. In another study, other muscle metabolite ratios, such as choline/lipid and creatine/lipid, were significantly different in chronic polymyositis and dermatomyositis cases compared to control subjects [25]. These abnormalities were evident in patients with normal as well as elevated CPK activities [25]. Further studies are needed to determine whether proton spectroscopy is an appropriate tool for disease activity assessment.

Abnormal metabolic profiles were also recorded in the urinary proton MR spectra of IIM patients. Levels of the muscle metabolites, such as creatine, choline-containing compounds, glycine, taurine and betaine, were all significantly higher than in controls [127]. High levels of urinary creatine were recognized early in this disease using standard methods for many decades [27, 128], but the widespread nature of other changes has not been previously reported. Elevated taurine levels in urine were also reported in other conditions, probably reflecting general muscle degeneration [127]. Creatine, choline-containing compounds, glycine and taurine levels were reduced with treatment in polymyositis and dermatomyositis patients, and their levels seemed to be related to clinical outcome [127]. Urinary proton MRS metabolic profiles may thus have the potential to be a non-invasive method for assessment of disease activity in IIM patients and to monitor the efficacy of therapy in an objective manner.

MRS (in particular phosphorus) in conjunction with MRI offers new avenues for assessing the biochemical status of diseased muscles in myositis patients. The changes observed using MRI and spectroscopy were determined to be more reliable than the conventional CPK activity, as abnormal anatomical and biochemical changes were often observed in clinically symptomatic patients with normal CPK activities [25, 109, 114]. MRS together with MRI may have the potential to evaluate the biochemical and anatomical changes that are significant in disease pathogenesis [129]. In particular, they may provide an easily quantifiable technique for assessing disease progression and response to therapy [129, 130].

Ultrasound

Several muscle groups were used for both diagnostic and follow-up evaluation in a few studies of IIM [88, 90]. This technique does not, however, seem to be a useful tool for follow-up studies as there was no correlation between echogenicity and muscle strength in the only longitudinal study performed to date [90]. Furthermore, ultrasound does not seem to be helpful for guidance of which muscle to select for biopsy for diagnostic purposes [88].

Summary

In conclusion, the IIM are a group of muscle disorders with a substantial number of patients who develop a chronic disability and a reduced quality of life due to persisting decreased muscle function as well as to side-effects of corticosteroid treatment. Until more controlled trials have been performed, we mainly have to rely upon interpretations of uncontrolled trials for treatment recommendations for patients with IIM. These studies support initial treatment with prednisone in starting doses of 0.75 mg/kg/day for $\sim$4 weeks with tapering doses according to muscle function thereafter. Because of the high corticosteroid doses that are required, an additional steroid-saving immunosuppressive would be optimal and controlled trials are of great necessity. By performing careful follow-up studies correlating clinical outcome with molecular findings in repeated muscle biopsies and MRS, an increased knowledge concerning the pathogenesis as well as the effect of treatment at a molecular level will be achieved. An increased knowledge of which molecules, e.g. cytokines and chemokines, are important in the inflammatory process will hopefully make it possible to develop more selective therapies for myositis patients, similar to the development of new treatment modalities which are currently being investigated in rheumatoid arthritis [131]. A rarely recognized aspect of the IIM is the possible metabolic disturbance as a cause of the persisting muscle weakness. The use of MRS to assess metabolic molecules provides a promising new means of disease activity assessment that needs to be further evaluated in follow-up studies. An important aspect of treatment that should be included in the rehabilitation programme of the IIM is active physical exercise, which was recently demonstrated not only to be safe, but also to improve muscle strength in myositis patients [71–75]. To facilitate the development of improved therapies, a validated disease activity measure would be very helpful. An international collaboration group could hopefully develop such a disease activity index for adult myositis, encouraged by the work which has already started for juvenile dermatomyositis [94].

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