Idiopathic Inflammatory Myopathies: Current and Future Therapeutic Options

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Summary: Idiopathic inflammatory myopathies (notably polymyositis and dermatomyositis) are relatively uncommon diseases with a heterogeneous clinical presentation. Only a few randomized, double-blind, placebo-controlled trials have been performed, measures to assess outcome and response to treatment have to be validated. Initial treatment options of first choice are corticosteroids, although rarely tested in randomized, controlled trials. Unfortunately, not all patients respond to them and many develop undesirable side effects. Thus, second line agents or immunosuppressants given in combination with corticosteroids are used. For dermatomyositis/polymyositis, combination with azathioprine is most common. In case this combination is not sufficient or applicable, intravenous immunoglobulins are justified. Alternative or stronger immunosuppressants, such as cyclosporine A, cyclophosphamide, methotrexate, or mycophenolate are also used. There are no defined guidelines or best treatment protocols agreed on internationally; therefore, the medical approach must be individualized based on the severity of clinical presentation, disease duration, presence of extramuscular features, and prior therapy and contraindications to particular agents. Approximately 25% of patients are nonresponders and continue to experience clinical relapses. Those are candidates for alternative treatment options and experimental therapies.

New immunoselective therapies directed toward cytokine modulation, immune cell migration, or modification of certain immune subsets (B- and T-cells) are a promising avenue of research and clinical application. Possible future therapeutic options are presented and discussed. **Key Words:** Idiopathic inflammatory myopathies, myosilis, therapy, polymyositis, dermatomyositis, inclusion body myositis.

INTRODUCTION

Myositis is the generic term for a relatively rare, heterogeneous group of acquired inflammatory muscle diseases that can lead to progressive restriction of mobility, as well as increase in morbidity, due to involvement of extramuscular organs. Treatment of inflammatory muscle diseases is challenging and can become extremely difficult in refractory cases.

Myositis is classified according to clinical, histological, and immune-pathological criteria. The key components of myositis diagnosis entail assessment of clinical features, serological tests, electromyography, and muscle biopsy changes (Table 1). Imaging procedures can aid to the diagnosis. Incidence of the three idiopathic inflammatory myopathies, polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM), together is around 1/100,000 (DM > IBM > PM). The key symptom of all three forms is muscle weakness, whereas sensibility and tendon reflexes are normally maintained. Although distribution of muscle weakness has a proximal-symmetrical pattern in PM/DM, IBM also occurs in distal muscle groups, especially foot extensors and finger flexors. Distribution can be asymmetrical (reviewed in Engel et al.,[1] Dalakas and Hohlfeld,[2] Goebels and Pongratz,[3] and Amato and Griggs[4]).

Up to 50% of patients have pain in muscles and/or hinges. All three forms may be associated with dysphagia, an effect of the respiratory and neck muscles. In PM and DM, even the heart may be affected, as seen by changes in electrocardiographic measurements, pericarditis, dilatative cardiomyopathy, and/or coronary failure, and the lungs may be affected as evidenced by interstitial lung disease. In DM, characteristic skin alterations occur in children sometimes, developing calcifications.

Recent studies with stricter application of histopathological diagnostic criteria show that polymyositis occurs far more seldom than had been claimed in earlier studies, making PM the rarest entity within all forms of idio-

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Table 1. *Clinical and Diagnostic Characteristics of PM, DM, and IBM*

	PM	DM	IBM
Women:Men ratio	2:1	2:1	1:3
Age at disease onset	>18 years	5–15 and 45–65 years	>50 years
Skin alterations	No	Yes	No
Muscle pareses	Proximal > distal, symmetrical	Proximal > distal, symmetrical	Proximal = distal, asymmetrical, predilection: finger flexors
Muscle pain	(+)	+	(+)
Muscle atrophies	+	(+)	++
EMG	Myopathic	Myopathic	Myopathic and neurogenic
CK	Up to 50×	Up to 50×	Normal up to <10×
Muscle biopsy	Peri- and endomysial infiltrates, invasion of non-necrotic, MHC class-I positive fibers by cytotoxic CD8 T cells	Perifascicular atrophy, perimysial and perivascular inflammatory infiltrates; deposits of complement on vessel walls	Infiltrate variable, endomysial, atrophic fibers, "rimmed vacuoles", eosinophilic inclusions
Immunohistochemistry	CD8 > CD4, macrophages	CD20-immune-reactive B cells, macrophages, CD4 cells	CD8 > CD4, macrophages
Electron microscopy		Tubulovesicular inclusion in vessel endothelium	Helical tubulofilaments (15–18 nm) in the sarcoplasma and in muscle fiber cores, fibrils, autophage vacuoles
Associated problems	Myocarditis, interstitial pulmonary disease, malignoma, other systemic diseases (collagenosis)	Myocarditis, interstitial pulmonary disease, malignoma, other systemic diseases (collagenosis)	Neuropathy
Response to therapy	Yes	Yes	No or only minimal

CK = creatine kinase; DM = dermatomyositis; EMG = electromyography; IBM = inclusion body myositis; PM = polymyositis.

pathic myositis.[5] Inclusion body myositis is the most frequent inflammatory myopathy in patients over age 50, ranging slightly behind dermatomyositis with regard to frequency of all ages. Various groups have proposed revised diagnostic criteria for idiopathic myositis, especially to enable a better standardization and validation of clinical trials and trial endpoints. This is particularly the merit of the International Myositis Assessment and Clinical Studies Group (IMACS).

Muscle MRI can be very useful in diagnosing and assessing activity in patients with myositis because of its sensitivity on measuring the tissue's water content. Muscle edema, as detected by MRI, correlates well with inflammatory changes. A comparison of the T1- and T2-weighted fat suppressed sequences is used to interpret whether weakness is attributable to ongoing inflammation (sometimes patchy), a mixed picture of both inflammation and damage, or muscle atrophy with fat replacement.

The cause of PM, DM, and IBM is unknown thus far.[2,6] While in PM, a T cell-mediated autoimmune process is assumed, the cause of DM is assumed to be driven by antibody-mediated effector mechanisms.[7,8] The autoantigen(s) directed against the immune reactions are merely unknown so far (reviewed in Chevrel et al.,[9] Hohlfeld,[10] Isenberg et al.,[11] and Suber et al.[12]).

In IBM, a degenerative process with accumulation of pathological protein fibrils, similar to the process in Alzheimer's disease, is currently discussed.[13] The trigger is unknown. It is assumed that this trigger initiates a cascade of degenerative and inflammatory events, including amyloid deposits, oxidative stress, abnormal signal transduction, and immune reaction (reviewed in Dalakas[14] and Askanas and Engel[15]).

The prognosis for myositis has improved over the past years. In the absence of malignity, the 5-year survival rates of adults with DM or PM is between 70% to 89%, according to literature sources (e.g., Engel et al.[1] and Airio et al.[16]). A retrospective study analyzed the disease course of 77 PM and DM patients.[17] Under immunosuppressive therapy, 40% of patients showed remission; a further 43% of patients showed improvement; and in 17%, the clinical symptoms exacerbated. Survival rates were about 83% after 1 year, 77% after 5 years. Among the causes of death were malignoma (47%) and pulmonary complications (35%). Prognosis of paraneoplastic myositis is essentially determined by the underlying malignant disease. Otherwise, poor prognostic factors that

are common to several studies include old age, nonwhite race, bulbar involvement, delayed treatment, and cardiovascular and pulmonary involvement.[18]

GENERAL CONSIDERATIONS FOR THE THERAPY OF MYOSITIS

The main objective of treatment is to improve muscle strength and to obtain remission, or at least clinical stabilization. Muscle strength, and clinical and laboratory criteria should be routinely assessed. Consensus about the assessment of disease activity confirms that several domains must be considered, namely: 1) global disease activity, by which some use patient/parent visual analogue scales; 2) muscle strength, by using manual muscle testing; 3) physical function, by using the Health Assessment Questionnaire/Childhood Health Assessment Questionnaire; 4) laboratory evaluation, by measuring at least two serum enzymes from creatine kinase, aldolase, lactatdehydrogenase, aspartate aminotransferase, or alanine aminotransferase; and 5) by determining extra-skeletal muscle involvement.[19]

Extended set measures can be added to each of these five domains to achieve greater accuracy, including dynamometry, maximum voluntary isometric contraction, and MRI (e.g., T2-weighted images, muscle biopsies, cutaneous assessment tools, and so forth).

As the patients' own perception of their quality of life is also important, it may be assessed by the 36-item short form.[19] Disease damage remains difficult to assess and a suitable index to agree and to be validated is awaited. An international consensus on disease activity and damage, partially validated, has just been published by the IMACS group.[20] In assessing disease activity, two indices were tested: 1) myositis intention to treat index, which consists of a modification of the British Isles Lupus Assessment Group and is based on the principle of the physician's intention to treat, and 2) myositis disease activity assessment visual analogue scale, by a series of 10-cm video-assisted surgeries completed by the physician to assess the patient in systems that may be affected in myositis. Both show initially good results, but with certain limitations and further need for validation. For the assessment of myositis-induced damage, a myositis damage index has been suggested. This index evaluates the extent and severity of damage in the different organs that might be affected, using modification of the Systemic Lupus International Collaborative Clinics/American College of Rheumatology (SLICC/ACR) damage index.

In addition, the myositis damage score (MYODAM) index has been developed. In this index, a myositis damage score, represented by a series of 10-cm video-assisted surgeries, is used to quantify the severity of damage in the various organs affected. However, a formal

validation and studies on its reliability are also being awaited.[20]

CURRENT THERAPY

Therapy of DM/PM

Pragmatically, therapy of myositis can be divided into three phases: 1) initial therapy, 2) maintenance therapy, and 3) long-term therapy.

Phase 1: Initial therapy. Corticosteroids are agents of first choice in DM, as well as in PM. Acute therapy usually starts with 1 to 2 mg/kg body weight for 2 to 4 weeks, followed by a slow dose reduction, and finally an alternating administration every other day. Most patients initially respond very positively. However, as the steroid doses are reduced in the course of therapy (and with it the adverse effects), additional administration of an immune suppressant becomes necessary in many cases, especially in cases with more severe affection. In the case of pronounced muscular symptoms, some authors recommend an initial high-dose steroid therapy (summary, Table 2).

Immunosuppressants are used for long-term therapy; a low-dose corticosteroid therapy, partly in combination with azathioprine, is often required for 1 to 3 years as relapse prophylaxis.[21] These therapeutic regimens, which in principle existed for decades, are mostly empirical or based on smaller therapeutical trials. There have not been any larger randomized, placebo-controlled, therapeutic studies so far.

Azathioprine, given in dosages up to 3 mg/kg body weight, is often initiated early in the disease course, particularly in patients with a more severe disease course (e.g., in patients with general weakness, respiratory impairment, or dysphagia). The delay of 3 to 6 months until onset of clinical efficacy has to be considered. Combination of corticosteroids with azathioprine is the most common combination in PM/DM therapy.

Methotrexat, a folic acid antagonist, given in a dose of 7.5 to 25 mg/week, operates faster than azathioprine, but has a higher toxicity level. One adverse effect may be pneumonitis, which might sometimes be difficult to distinguish from interstitial lung impairment (e.g., in JO-1 syndrome). Therapy should start with the administration of 7.5 mg once a week orally. After 3 weeks, the dose may be raised by 2.5 mg/week up to a target dose of 10 to 25 mg/week, depending on the clinical symptoms. A maximum dose of 25 mg/week should not be exceeded.

Cyclosporine in a dose of 2.5 to 5 mg/kg body weight, administered in two doses, depending on plasma level and efficacy, can also be used. Cyclosporine inhibits T-cell activation and is well known in the therapy of transplant rejection. The regimen used in myositis requires good compliance of the patient, as well as regular controls of serum level and renal function, be-

Table 2. *Pragmatic Therapy of Myositis: PM/DM*

Indication	Medication	Dose	Evidence Level of Recommendations
PM/DM with severe manifestation	Methylprednisolone i.v.	500 mg/day for 3–5 days	↔
PM/DM, more moderate form and/or continuation after i.v. therapy in the case of severe manifestation	Prednisone p.o.	*Initially:* 1–2 mg/kg body weight/day upon clinical response: weekly reduction by 5–10 mg of daily dose and/or after "alternate day program" *Maintenance dose:* 5–10 mg/day or 20 mg every other day	
PM/DM with severe manifestation in addition to oral prednisone	Azathioprine p.o. Immunglobulins i.v.	2–3 mg/kg body weight/day 0.4 g/kg kg/day for 5 days Repeat every 6–8 weeks depending on clinical symptoms	↔ ↑ (DM) ↔ (PM)
PM/DM with severe manifestation and refractory cases in addition to oral prednisone	Methotrexate p.o.	*Initially:* 7.5 mg/week Dose increase dependent on clinical symptoms after 3 weeks by 2.5 mg/week *Target dose:* 10–25 mg/week	↔
	Ciclosporine p.o.	2.5–5 mg/kg body weight/day (corresponding to plasma level and efficacy)	↔
	Mycophenolate p.o.	2×1 g/day (ca. 20 mg/kg body weight). Plasma level ("through level"): 1–2 mg/L	↔
	Cyclophosphamide p.o.	1–2 mg/kg body weight/day	↔
	Cyclophosphamide i.v.	0.5–1.0 g/m^2 body surface	↔
	Rituximab i.v.	$2 \times 1,000$ mg (span of 2 weeks). Repeat after 6–9 months or after clinical response	↔
PM/DM with extramuscular organic manifestation	Cyclophosphamide p.o.	1–2 mg/kg body weight/day	↔
	Cyclophosphamide i.v.	0.5–1.0 g/m^2 body surface	↔
	Rituximab i.v.	$2 \times 1,000$ mg (span of 2 weeks) Repeat after 6–9 months and/or after clinical response	↔
Most severe therapy-resistant PM/ DM with/without extramuscular organic manifestation	Alternative treatment options or individual treatment options (e.g., rituximab, tumor necrosis factor-alpha receptor-antagonists, tacrolimus/FK507, alemtuzumab)		↔

↑ = recommendation is based on at least one adequate, valid clinical study (e.g., randomized); ↔ = no valid and clinical studies or safe evidences are available; i.v. = intravenous; p.o. = per os; DM = dermatomyositis; IBM = inclusion body myositis; PM = polymyositis.

cause cyclosporine shows variable resorption and a dose-related nephrotoxicity. The latter occurs in most cases only in doses from 5 to 6 mg/kg body weight/ day. Existing kidney diseases and arterial hypertonus increase the risk of a renal impairment triggered by cyclosporine.

Administration of cyclophosphamide (1 to 2 mg/kg body weight/d orally, 0.0 to 1.0 g/m^2 i.v.) in DM/PM is only necessary when common therapy has failed, or in the case of anti-synthethase syndromes with secondary alveolitis.[22–24] Recent case reports also show successful treatment of therapy-refractory myositis with mycophe-nolate mofetil (2 g/day) (e.g., Majithia and Harisdan-gkul,[25] Choudry et al.,[26] and Schneider-Gold et al.[27]). This substance selectively blocks the purine synthesis in lymphocytes, and thus inhibits their proliferation. The most important side effects of mycophenolate mofetil include chronic diarrhea, hemolytic anemia and edema. Mycophenolate mofetil is an option when azathioprine fails and is increasingly preferred to azathioprine in transplantation medicine. Recently, increasing numbers of malformations were registered in pregnant patients with kidney transplants and preceding mycophenolate mofetil treatment during pregnancy. However, individual

cases of progressive multifocal leukoencephalopathy (PML) have been observed in immune-suppressed patients (lupus erythematodes). One case of a primary CNS lymphoma under mycophenolate mofetil therapy has been reported.[28]

Intravenous immunoglobulins in patients not responding to corticosteroids/azathioprine, therapy with intravenous immunoglobulins (IVIG, 2g/kg body weight every 1 to 2 months) is justified. Convincing beneficial effects of IVIG therapy have especially been shown for DM.[29] In juvenile DM, immunoglobulins are often administered very early to prevent immunosuppressive strategies with potentially numerous side effects, but the success is not reliable.[30] Also in therapy-resistant PM, cases of successful treatment with immunoglobulins have been published.[31] However, these results are too inconsistent to allow IVIG as a recommendation for primary therapy (see Dalakas[32]).

Phase 2: Maintenance therapy. This therapy depends on initial treatment response, but data shows that after approximately 6 months, corticosteroid doses should be reduced below "Cushing level." An alternating administration is preferred (every other day). If after 3 months, the steroid dose is still clearly above the Cushing level and further reduction does not seem possible without the risk of a relapse, immunosuppressants (see previously mentioned) (Table 2) should be given in addition. The first choice agent here is azathioprine. In childhood DM, however, methotrexate is preferred to azathioprine.

Phase 3: Long-term therapy. After reaching clinical stabilization, low-dose, long-term therapy is normally necessary. In most cases, this is given as a combination of a corticosteroid and an immunosuppressant. For relapse prophylaxis, this medication is given for 1 to 3 years, and even longer, where appropriate. During long-term therapy with corticosteroids, a reappearance of muscle weakness might occur when creatine kinase activity is normal or unchanged, and this is possibly the occurrence of a steroid myopathy. Sometimes this might be hard to distinguish from the initial myositis symptoms. In addition, symptoms are aggravated by immobilization and accompanying systemic disease. In such cases, reduction of corticosteroids should be considered under careful clinical observation. An increase in creatine kinase activity and pathological spontaneous activity in the electromyography are indicators voting against steroid myopathy. If clinical decision is ambiguous, a re-biopsy should be conducted. However, steroid myopathy is rather improbable if there are no other signs of iatrogenic Cushing symptoms, such as osteoporosis, cushingoid phenotype. Furthermore, it is important to distinguish between existing inflammatory disease activity and residual disease after active DM/PM ("burned out stages").

From experience, problems during therapy occur when many different substances have been used, but none of them has been administered long enough or in appropriate doses. Attenuation of the known side effects of a long-term corticoid therapy, such as osteoporosis, and gastric ulcera, can be achieved by giving antazida, proton pump inhibitors, and by substitution of calcium and vitamin D.

Therapy of sporadic IBM

So far, sporadic inclusion body myositis (sIBM) has proven to be relatively refractory to therapy. Corticosteroids and immunosuppressants have (with few exceptions) proven to be ineffective. However, no controlled trials, neither about efficacy of corticosteroids or about efficacy comparison of the various immunosuppressive substances, exist in sIBM. Overall, response of sIBM to immunosuppressive therapy has been discussed very controversially. Until today, only a few authors consider an immunotherapeutic treatment (i.e., corticosteroids plus azathioprine or methotrexate) attempted over 3 to 6 months as justified (e.g., Mastaglia and Zilko[33]).

Numerous negative or minimally encouraging trial reports exist for immunomodulatory and/or immunosuppressive strategies of sIBM. Examples include controlled trials with betainterferon[34,35] or a 48-week trial with methotrexate (http://www.clinicaltrials.gov/ct/show/NCT00033891).

A placebo-controlled pilot study over 12 months with anti-thymocyte globuline (ATG-Fresenius, Fresenius AG, Bad Homburg, Germany) and methotrexate in 10 patients showed a constant muscular strength in the anti-thymocyte globuline/methotrexate group compared with an exacerbation of 15% in the placebo group. There were no severe side effects. The authors proposed application of this regimen in "young" IBM patients who show a rapidly progressive disease course.[36]

Therapeutic benefit of repetitive immune adsorption has been described in a patient with sIBM and monoclonal gammopathy.[37] This might be considered as a therapeutic option if there are immunological disturbances apart from IBM.

A controlled pilot study with 19 sIBM patients with oxandrolon (Oxandrin, Savient Pharmaceuticals, Inc., East Brunswick, NJ), a synthetic androgen, showed, at best, a marginal effect with regard to muscular strength.[38]

Alemtuzumab (Campath-1), a monoclonal antibody, is directed against CD52, a cell surface molecule present on various immune cells (particularly T cells, B cells, and dendritic cells) and inducing selective immune depletion after intravenous application. Alemtuzumab was used in a controlled study in patients with sIBM. Clinically, this immunoselective treatment showed no significant effects

Table 3. *Myosits: Synopsis of Most Important Treatment Recommendations*

The idiopathic myositis syndromes consist of polymyositis (PM), dermatomyositis (DM) and sporadic inclusion body myositis (sIBM).

A causal therapy of the dysimmune/idiopathic myositis syndromes is not established.

Therapeutic regimens are mostly empirical or are based on smaller therapeutic studies

Therapy of PM/DM:

PM and DM can be controlled with immunosuppressive therapy in the majority of cases.

For initial therapy, corticosteroids are the drug of first choice.

For long-term therapy, a low-dose corticosteroid therapy is often needed, partly in combination with immunosuppressive therapy with azathioprine. Relapse prophylaxis is needed for 1 to 3 years or longer.

For patients that do not respond to corticosteroids/azathioprine, a treatment with intravenous immunoglobulins is justified.

Stronger immunosuppressive treatment regimens are used in patients with severe extramuscular organ manifestation.

Newer immunoselective therapies can be successful in cases of refractory disease. One option is immunoselective, B-cell directed treatment with anti-CD20 antibody rituximab. Treatment with rituximab can help to reduce concomitant immunotherapies. Antibodies possibly associated with myositis syndromes neither predict nor correlate necessarily with the therapeutic response to anti-CD20 treatment.

Treatment of Sporadic IBM:

sIBM is often characterized by a progressive disease course and therapeutic resistance.

Some authors recommend an initial treatment trial with monthly intravenous immunoglobulins, which can induce stabilization of disease.

A short-term (approximately 6 months) immunsuppressive treatment attempt can be considered in analogy to the therapy of PM/DM.

General Remark:

Regular control of muscular strength is needed to judge treatment response and necessary adaptation of immunosuppressive treatment.

Laboratory Measures:

Especially creatine kinase can be used as individual marker of treatment response.

In IBM, creatine kinase can be lowered without any clinical relevance.

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on muscle strength, but the inflammatory infiltrations in the muscle were reduced.[39]

For IVIG, controversial reports exist. Dalakas et al.[40] could prove a significant improvement of dysphagia in a controlled study with 10 sIBM patients. In six patients, but not in the whole treatment group, there was a functional recovery with regard to muscle strength and everyday activities.[40] In a double-blind, placebo-controlled study, a significant improvement of daily activities by 11% with constant muscle strength could be achieved in 22 sIBM patients in the course of 1 year.[41] In contrast, combination of steroids with IVIG did not show any efficacy in a controlled study in 36 sIBM patients.[35]

Depending on the individual disease course, a therapeutic attempt with IVIG over 6 months appears reasonable. After 6 months, therapeutic success should be clinically evaluated by improvement, stabilization, or further progression, and also evaluated electrophysiologically (e.g., decrease in pathological spontaneous activity) to be able to provide a valuable basis for the decision on therapy continuation.

Table 3 summarizes the most important therapeutic recommendations and "take home" remarks for the therapy of DM/PM as well as sIBM. With regard to treatment recommendations and levels of evidence, it should be kept in mind that many studies are based on only very few patients.

RECENT REPORTS, ONGOING STUDIES AND EXPERIMENTAL THERAPEUTIC OPTIONS IN IDIOPATHIC INFLAMMATORY MYOPATHIES

A number of novel therapies are currently being investigated in clinical trials. Furthermore, numerous smaller series have provided preliminary evidence of potential use of certain substances in the treatment of inflammatory myopathies.

Mycophenolate mofetil has been promoted as a helpful immunosuppressive agent in the therapy of treatment-refractory myositis (PM/DM). Seven patients have been reported by Majithia and Harisdangkul in 2005.[25] Another six patients have been reported by Pisoni et al.[42] in 2007. As previously indicated, the risk of opportunistic infection seems increased in combination with corticosteroids.[43]

Three tumor necrosis factor-alpha (TNF-alpha) inhibitors (infliximab, adalimumab, and entanercept), which are approved for therapy of rheumatoid arthritis and/or psoriasis arthritis, ankylosing spondylosis, or inflammatory bowel disease, are currently being tested in DM and PM. Etanercept was applied in 9 patients with IBM, and after 6 and 12 months, there was no effect seen in comparison to natural controls.[44]

Myositis with interstitial lung disease plus concomitant positivity of aminoacyl transfer RNA synthetase antibodies

(especially JO1) seem to respond positively to calcineurin inhibitors (cyclosporine and tacrolimus).[45–47]

The monoclonal antibody anti-CD52 (alemtuzumab, CAMPATH-1) has been applied in a controlled study in patients with sporadic IBM. Clinically, these immune-selective treatments did not show significant positive effects on muscle strength; however, inflammatory infiltrates in muscles (seen in repetitive biopsies) were reduced.[39]

Recent studies point to an important role for B cells and antibodies in the pathogenesis of dermatomyositis, but less so in polymyositis and inclusion body myositis (reviewed in Greenberg[48]). Rituximab, a monoclonal antibody directed against CD20 expressed on B cells (anti-CD20), has already been used in a number of smaller case series as well as open observations. The success of this therapy has partly been demonstrated[49–56] (see http://www.clinicaltrials.gov/ct/show/NCT00106184 and http://www.clinicaltrials.gov/ct/show/NCT0007978. therapy). Several case reports[55,57] and an open-label pilot study[58] suggest that rituximab may be effective in the treatment of refractory polymyositis. A positive therapeutic response of myositis associated with lung disease (i.e., interstitial lung disease) and concomitant anti-aminoacyl transfer RNA synthetase antibodies (especially anti-JO1) was observed by Lambotte et al.[55] as published in their report in 2005. Rituximab also has potential in the treatment of both myositis-specific auto-antibody-positive and -negative juvenile dermatomyositis, according to results from a case series ($n = 4$) of pediatric patients.[49] For adult patients with dermatomyositis, evidence of efficacy is mixed. Findings from case reports,[54,57] a case series,[51] and an open-label pilot study ($n = 7$)[56] suggest that rituximab can markedly improve the musculoskeletal and cutaneous symptoms of the disease; in contrast, results from another open-label pilot studies ($n = 8$)[50] suggest that rituximab has limited effect on the skin. Titers of antibodies associated with these syndromes (e.g., anti-Jo) do not necessarily predict or correlate with the clinical response to rituximab. This interesting and important therapeutic strategy is currently being tested in an NIH-supported trial in therapy-refractory DM and PM patients (http://www.clinicaltrials.gov/show/NCT00299819).

Of note, therapies with monoclonal antibodies have been associated with severe adverse effects. Specifically, the potential risk of opportunistic infections (e.g., progressive multifocal leukoencephalopathy occurred in association with anti-CD20 treatment) or the occurrence of life-threatening autoimmune disorders (idiopathic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, occurred in association with anti-CD52, alemtuzumab) should serve as a note of caution.

FUTURE THERAPEUTIC AVENUES AND OPTIONS

Albeit a significant number of patients with inflammatory muscle disease respond adequately to treatment with corticosteroids and immunosuppressive or modulatory agents, investigations continue for more effective drugs with fewer side effects. Furthermore, recent findings elucidating the immunopathogenesis open new avenues for therapeutic targets or strategies (e.g., Dalakas[14] and Greenberg[48]).

One could formally separate those as approaches of: 1) general immunosuppression or immunomodulation, 2) immune-specific intervention, and 3) individualized therapy (immune-specific intervention based on individual pathogenic mechanisms encountered in one patient).

The first category (immunosuppressive or immunomodulatory interventions) assumes that the immune system plays a key role in the pathogenesis of PM/DM/IBM. Therefore, agents with immunosuppressive or immunomodulatory properties, but with a beneficial side effect profile, are attractive for studies in myositis. This would include a number of already approved FDA (FDA) drugs with indications in other autoimmune diseases, but thus far is not reported as used off-label or in trials for inflammatory myopathies. With sufficient interest, clinical trials of such drugs could advance rapidly. Such approaches would not be considered as a causal treatment, but might offer substances with a better risk-benefit profile, potentially achieving higher rates of remissions, especially in the inflammatory myopathies PM/DM.

The second category would be interventions that are immunoselective. This is certainly a very attractive and promising area of research, assuming that key pathways or molecules or immune subsets involved in the pathogenesis of DM *versus* PM *versus* IBM could be selectively targeted.

Pathogenetic models that assume that T cells injure muscle fibers in polymyositis and inclusion body myositis promote agents or strategies to affect T-cell function. New biologic agents targeting T-cell activation, transmigration and antigen recognition may be rewarding. Such immunoselective or semi-specific immunotherapies could be accomplished with biotechnologicals directed against co-stimulatory molecules (e.g., CD28, CTLA-4, inducible costimulatory signal ligand/inducible costimulatory signal pathway, B7-H1/PD-1 pathway), adhesion molecules (e.g., integrins/lymphocyte function associated antigen-1/intercellular adhesion molecule), immune cell subpopulations (e.g. CD52, alemtuzumab), certain cytokines (e.g., tumor necrosis factor-alpha, interleukin-6) or T-cell receptor-induced pathways (e.g., anti-CD3). Efalizumab[59] and alefacept[60] are both approved FDA drugs for the treatment of psoriasis. Abatacept[61] is an approved FDA biotechnological for

rheumathoid arthritis with efficacy also in psoriasis. These drugs were all designed to disrupt interaction of T cells with other cells. Efalizumab interferes with T-cell adhesion both to keratinocytes and endothelium via targeting CD11a. Furthermore, it disrupts the T-cell interaction with dendritic cells and blocks the cutaneous entry of memory cytotoxic T cells.[62–64] All functions make its potential feasibility plausible in myositis. Alefacept targets cells with high expression of CD2, to which LFA-3 binds. Alefacept is a fusion protein made from lymphocyte function-associated antigen-3 (LFA-3).[60] Abatacept inhibits the T-cell surface molecule CD28 and its interaction with the most important co-stimulatory ligand CD80 and CD86, expressed on all professional antigen-presenting cells, including dendritic cells and B cells. This CTLA-4 IG is an interesting example of how to bridge basic immunology with clinical application, already successfully pursued in rheumatoid arthritis and psoriasis. Whether this substance (abatacept) or a similar investigational drug (belatacept[61]) make their way into the treatment of myositis remains to be shown in the future.

The interferon-alpha/beta pathway and its particular link to the pathogenesis of dermatomyositis,[65] has encouraged thoughts to target this pathway in clinical situations. Examples for disrupting the interferon-alpha pathway have been promoted in the treatment of systemic lupus erythematodes and several strategies have been considered (e.g., Schmidt and Ouyang[66] and Stewart[67]). Certain biotechnologicals directed against interferon-alpha are currently undergoing trials in systemic lupus erythematodes. Furthermore, a monoclonal antibody against BDCA-2[68] and oligonucleotides that inhibit TLR-9 function[69] could also be used to reduce interferon-alpha/interferon-beta production. Of note, the functional implications of studies suggesting an important role of this pathway in the pathogenesis of DM, but to some extent also in IBM and PM, should be corroborated by other groups under preclinical conditions before starting any extensive clinical program.

Cell-based therapies and strategies to modulate the function of dendritic cells or suppressive T-cell population could be considered as well. Those approaches include vaccination with genetically or cellularly engineered myeloid dendritic cells designed to induce tolerance, or the development of drugs that promote the immunosuppressive properties of immature myeloid-dendritic cells. Furthermore, the recent characterization of regulatory T-cell populations involved in the pathogenesis of autoimmunity has been a rewarding area of basic and clinical research. Regulatory T cells also might be an interesting cellular target for the treatment of inflammatory myopathies, the corollary being that reconstitution of endogenous immune tolerance or promotion of repair could be achieved by continuous or temporary upregulation of T-regulatory cells (quantitatively or qualitatively). These treatment attempts are of considerable interest also in other autoimmune disorders, including juvenile diabetes or multiple sclerosis.[70]

Finally, the ideal therapy for myositis would be tailored for the individual driving pathogenetic mechanism (see category 3 as previously mentioned). Such highly individualized therapy would take into account the disease entity and the driving pathogenetic mechanisms in relation to the status of the disease. They could include antigen-specific therapies or consider relevant key molecular targets, and deduced from this, the application of appropriate treatment or treatment combinations. Although this is certainly one of the "holy grails" or "dreams" of any immune therapy of autoimmune disorders, the possibilities and realistic chances to do so in idiopathic inflammatory myopathies are pretty far-fetched. Specifically in myositis, the driving antigen or antigens are merely unknown. However, one could assume to figure out the key pathogenetic elements based on gene array or chip analysis from muscle biopsy specimens in addition to peripheral blood. This approach had already elegantly shown the differences between the three key clinical entities IBM, PM, and DM[71] and could theoretically also be a helpful addition in terms of therapeutic decision making. However, such "idealistic" approaches have to be carefully prepared on the basis of large international collaborative efforts with significant patient numbers. It is assumed that this ideal goal of any immune therapy might not be reached within the next decade.

Taken together, the emerging therapeutic targets deduced from preclinical studies on the immunopathogenesis (and genetics) of the idiopathic inflammatory myopathies, together with the advent of biotechnologicals opens multiple avenues for future therapeutic options. However, the validation of assessment criteria and an international consensus on robust readouts to monitor damage from myositis and clinical response profiles from any therapy have to be consolidated before any sophisticated immune intervention or therapeutic strategy can be successfully established for a broad, but heterogeneous array of myositis patients. However, large and international collaborative efforts of various clinical experts, together with research units, are needed to bridge the gap between basic research and optimal clinical therapy.

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