# Novel approaches in the treatment of myositis and myopathies

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***Abstract:*** The inflammatory myopathies are a heterogeneous group of disorders characterized by muscle weakness and inflammation. Although no standard therapeutic guidelines exist, traditional treatment has included corticosteroids and a variety of second-line immunosuppressants. As treatment of refractory disease has been difficult, newer agents and approaches have been used with varying response. The advent of standardized treatment response criteria by the International Myositis Assessment and Clinical Studies (IMACS) group has helped investigators to evaluate and compare clinical trial outcomes in a more rigorous fashion. The use of intravenous immunoglobulin (IVIG), rituximab, biologic agents including tumor necrosis factor (TNF) inhibitors, stem-cell transplantation, gene therapy, and vascular occlusion resistance training are reviewed here. As our understanding of disease pathogenesis at the immunologic, genetic, and molecular level expands, the discovery of novel therapeutic targets hold promise for the successful treatment of these conditions.

***Keywords:*** gene therapy, idiopathic inflammatory myopathies, IVIG, novel approaches, rituximab, stem-cell transplantation

## Introduction

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of disorders of unknown etiology that include dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), and the more recently described entity, immune-mediated necrotizing myopathy. They are characterized by clinically significant muscle weakness, elevated muscle enzymes, electromyographic changes, and, in some instances, characteristic histologic changes with cellular infiltrates on muscle biopsy. They have been associated with myositis-specific antibodies and display a variable response to a host of immunosuppressive medications. Treatment of IIMs has been challenging without a standardized regimen thus far. While the advent of standardized treatment response criteria by the International Myositis Assessment and Clinical Studies (IMACS) group has helped investigators to evaluate and compare clinical trial outcomes in a more rigorous fashion [Hak *et al.* 2011], there has been a lack of large clinical trials demonstrating efficacy of medications. In addition, the rarity of these conditions with heterogeneity of both the diseases and response to treatment contribute to the complexity.

Treatment has largely been off-label based on clinical expertise and experiential reports. Traditional first-line medications remain to be corticosteroids, with second-line agents employed as steroid-sparing or due to a lack of durable effect. These second-line immunosuppressants include azathioprine, methotrexate, mycophenolate mofetil, leflunomide, cyclophosphamide, tacrolimus, cyclosporine, tumor necrosis factor (TNF) inhibitors, and intravenous immunoglobulin (IVIG). We consider refractory disease to be one that fails to respond to steroids and at least two other immunosuppressants. As our understanding of these diseases evolves, newer agents that show promise for refractory cases are being employed.

It is the goal of this review to discuss novel agents described and new applications of more established treatment over the last 3 years. A Medline search was employed of all relevant articles published from 2009 to 2011 which included case reports, clinical trials, experimental data, expert opinion, and reviews. Search terms included 'novel treatment', 'therapy', 'idiopathic inflammatory myopathies', 'myositis', 'dermatomyositis', 'polymyositis', 'inclusion body myositis', 'rituximab',

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'IVIG', 'TNF', 'myostatin', 'follistatin', and 'gene therapy'. Only those in English were included. Retrieved articles were critically analyzed and references were cross-checked to provide a comprehensive and up-to-date review of the topic. Studies that predate this specified time interval are beyond the scope of this review.

## Intravenous immunoglobulin

IVIG exerts diverse effects on the immune system at multiple levels which have allowed for its use in immune-mediated disease including the inflammatory myopathies [Quick and Tandan, 2011; Hartung *et al.* 2009]. It has been used off-label for a number of years as salvage therapy in refractory PM/DM [Donofrio *et al.* 2009; Katz *et al.* 2011]. More recently, a newer case series describes a particular benefit in myositis complicated by steroid-resistant esophageal involvement [Marie *et al.* 2010]. The favorable outcomes seen suggest that steroids in combination with high-dose IVIG be considered first-line treatment of life-threatening esophageal involvement. In severe interstitial lung disease (ILD)-associated PM, a case report [Bakewell and Raghu, 2011] showed an improvement following three doses of monthly IVIG in a patient with early disease. There was a complete resolution of fibrotic changes on high-resolution computed tomography with sustained remission after 2 years of follow up with no other immunosuppressants used. The authors suggest that IVIG be considered as first-line treatment especially when there is significant pulmonary involvement. This was further supported by a response to this report [Diot *et al.* 2011] in which a similar ILD-PM case was described, this time unresponsive not only to initial steroids but also to cyclophosphamide. Following infusions of IVIG, this patient also had a dramatic improvement in lung function. Still yet another area where the use of IVIG may be explored is in pregnancy-associated DM. In concurrence with two previous case reports of successful use of IVIG in pregnant patients with DM, Linardaki and colleagues described a patient treated with combined steroids and IVIG during pregnancy with symptom resolution and no adverse effects [Linardaki *et al.* 2009]. The last dose of monthly IVIG was given 15 days after delivery. Both mother and infant remain disease free after 6 years of follow up, with the mother on no further medications for DM.

An interesting report [Recher *et al.* 2010] highlights the unexpected beneficial effect of low-dose IVIG in a patient with IBM. Taken together with a similar earlier case report, this may be a strategy that can be explored in IBM, given the prohibitive costs associated with high-dose treatment that often fails to produce results in this subgroup of patients. Nevertheless, in our personal experience, IVIG has failed to be of benefit in our IBM patients. In juvenile dermatomyositis (JDM), a retrospective study identified 8 patients who were able to avoid steroid treatment with the use of IVIG +/- additional immunosuppressants including methotrexate [Levy *et al.* 2010]. This would have important implications especially in the pediatric population for whom prolonged exposure to steroids has known significant consequences.

Intravenous infusion has been the most common route of administration of immunoglobulins (Ig) in autoimmune diseases. Recently, a study [Danieli *et al.* 2011] reported the use of subcutaneous IVIG in 7 patients with active and refractory PM or DM. Subcutaneous Ig (SCIg) was administered at home by programmable pump after a period of training. The IVIG monthly dose of 2 g/kg was fractioned into equal doses given subcutaneously at weekly intervals. All patients showed a favorable treatment response which the authors feel lends support to the subcutaneous route of administration of Ig. Advantages of SCIg include no need for venous access, more stable day-by-day serum IgG levels, better resistance against infections, home-based self-administration requiring minimal skills, rapid infusions at a speed of 20–30 ml/h, and decreased risk for fluid overload or hyperosmolarity [Rezaei *et al.* 2011]. This may be a practical and economic alternative that is worth further exploration.

## Rituximab

Rituximab is a chimeric, murine/human monoclonal antibody directed against the CD20 antigen found on the surface of B lymphocytes which has found application in a variety of autoimmune conditions including rheumatoid arthritis (RA) and systemic lupus erythematosus. The premise for use in IIMs has included the presence of disease-specific antibodies, immune complex deposition and presence of B cells in inflammatory infiltrates of involved muscles [Majmudar *et al.* 2009].

There have been several case reports describing the successful use of rituximab in DM and PM mainly in cases refractory to conventional therapy

including IVIG [Majmudar *et al.* 2009; Mahler *et al.* 2011]. It seems there is a favorable trend in patients with myositis-specific antibodies including anti-Jo1, which appears in keeping with the mechanism of action of the drug [Frikha *et al.* 2009]. There is particular note of successful use with skin-predominant DM [Joshi *et al.* 2011], and in ILD in the antisynthetase syndrome [Sem *et al.* 2009]. In one case report [Vandenbroucke *et al.* 2009], ILD which was the remaining unresponsive aspect of the disease responded favorably to rituximab initiation. In IIM associated with signal recognition particle (SRP), a case report [Whelan and Isenberg, 2009] showed no benefit, but a larger case series [Valiyil *et al.* 2010] showed good response with improvement in manual muscle strength and/or decline in creatine kinase (CK) levels in six out of eight patients treated with rituximab. In immunosuppressive naïve dermatomyositis, one case showed sustained remission after only one course of rituximab (1000 mg on days 0 and 14) [Haroon and Devlin, 2010].

In the Auto-Immunity and Rituximab (AIR) registry in France, patients with refractory IIM (unresponsive to at least one immunosuppressant) were analyzed for patient characteristics, rituximab indication, regimen and tolerance [Couderc *et al.* 2011]. Thirty patients with PM, DM, and the antisynthetase syndrome were included. Rituximab was found to be effective in over 50% of patients on the basis of CPK levels, steroid dose, and physician opinion. Although there was an absence of standardized treatment and control group, with a small population size and short follow up, there was a trend to benefit. This lends further support to previous case reports of successful use of rituximab in IIMs.

The largest randomized controlled trial to date with regards to the use of rituximab in myositis (RIM trial) was presented as an abstract at the American College of Rheumatology meeting [Oddis *et al.* 2010]. As of the writing of this review, the trial has not yet been published in full manuscript form. This large NIH-funded trial included 200 DM/PM adult and pediatric patients who were refractory to both steroids and an additional immunosuppressant. Both groups were given two doses of rituximab (1 g 1 week apart). One group received the drug first and placebo 8 weeks later while the second group received placebo first followed 8 weeks later by rituximab. It was the 'time to beginning active rituximab' which was randomized with a primary endpoint of time to achieve improvement between the two groups. Owing to the inclusion of pediatric patients, a short 8-week run-in phase for the placebo group was required. This may have been too short to allow a distinction between the treatment and placebo curves to be seen. Although both the primary and secondary endpoints were not met as there was no significant difference between both groups, 83% of patients met the IMACS definition of improvement in the trial. It is our conclusion that this may be taken as additional support for the use of rituximab in myositis and suggests the possibility of a flaw in study design rather than actual treatment failure.

Rituximab represents the most widely used of the B-cell-directed therapies. The chimeric nature of the antibody may account for some of the infusion reactions associated with the drug. Humanized anti-CD20 molecules including ocrelizumab, ofatumumab, and veltuzumab are in development and may prove to have better side effect profiles [Levesque, 2009]. A variety of B-cell-directed agents are also in development including those targeting CD22, CD19, CD40-CD40L, B-cell activating factor (BAFF), and A proliferation-inducing ligand (APRIL). Although there is much excitement in testing these agents and finding application in a variety of diseases, many questions remain as to their optimal use in clinical practice as well as the role of B cells in disease pathogenesis. Whether they will supplant the use of Rituximab remains to be seen.

## Biologics

### *TNF inhibitors*

TNFα offers a potential therapeutic target as it has been proposed to play a role in the pathogenesis of inflammatory myopathies although somewhat ill-defined. Small uncontrolled series using various TNF inhibitors have shown mixed results [Stubgen, 2011]. As such, they have not been considered to represent consistently valuable options for either drug-naïve or refractory IIMs. A recent well-designed randomized placebo-controlled trial of etanercept in dermatomyositis was conducted [Muscle Study Group, 2011]. Eleven subjects, including one from our institution, were randomized to receive etanercept 50 mg SC weekly for 52 weeks and 5 to placebo with a standardized ('forced') tapering of steroids as tolerated during the first 24 weeks of the study.

Principal outcomes were adverse events, time from randomization to treatment failure (inability to wean off prednisone), and average prednisone dose after 24 weeks. All patients on placebo were treatment failures while 5 out of 11 in the etanercept group were successfully weaned off prednisone. A steroid sparing effect was noted. The median average prednisone dose after 24 weeks in the etanercept group was 1.2 mg/day *versus* 29.2 mg/day in the placebo group. The strength of this study was its trial design. The demonstration of successful steroid taper has clinically significant meaning. The limitation of this study was that its initial rigorous inclusion criteria of treatment-naïve patients or only those who had taken prednisone less than 2 months precluded adequate recruitment and necessitated later relaxation of the inclusion criteria to include those with more refractory disease. In total, only 16 of 40 planned patients were able to be enrolled. Nevertheless, these encouraging findings suggest that further investigation of etanercept, and other TNF- inhibitors, in myositis is needed.

### *Abatacept*

Abatacept is a selective co-stimulation inhibitor that inhibits binding of CD28 expressed on effector T cells reducing T-cell activation. A patient with polymyositis refractory to conventional treatment who was later on tried on abatacept had a good clinical response [Musuruana and Cavallasca, 2011].

### *Alemtuzumab*

Alemtuzumab is a humanized monoclonal antibody targeting CD52 on lymphocytes. A proof of principle study was conducted to examine whether alemtuzumab in IBM depletes peripheral blood lymphocytes, endomysial T cells and alters natural course of disease in a group of 13 patients [Dalakas *et al.* 2009]. Results of this small and uncontrolled study were promising in that one series of infusions was able to slow down progression of disease (as compared with natural history) up to 6 months, produced improvement in strength in some patients and reduced inflammation.

### *Tocilizumab*

Interleukin 6 (IL-6) appears critically involved in the development of polymyositis and its blockade warrants further investigation for the treatment of refractory cases [Okiyama *et al.* 2009]. Two patients with PM refractory to multiple immunosuppressants were started on a trial of tocilizumab, a humanized anti-IL-6 receptor antibody [Narazaki *et al.* 2011]. There was a normalization of CK levels during treatment. No information regarding follow up and muscle strength was provided, however.

### *Anakinra*

An increased expression of IL-1 in muscle tissue has been seen in patients with inflammatory myopathies, and treatment with an IL-1 receptor antagonist may be an emerging strategy. A small open-label pilot study with anakinra, 100 mg subcutaneously per day, was undertaken in 15 patients (PM, DM, and IBM) with treatment-resistant disease [Dorph *et al.* 2009]. Improvement as defined by the IMACS criteria was seen in seven patients (three with PM, three with DM, and one with IBM). A follow-up study was done probing the biological explanation for improvement in responders focusing on effector T-cell function [Zong *et al.* 2011]. The authors' findings indicate that anakinra might favor T-cell differentiation into Th1 rather than Th17 as indicated by more interferon gamma (IFNγ) and less IL-17A secretion.

### *MEDI-545*

Type 1 IFN has gained focus in the treatment of IIMs with the finding that there is marked overproduction of type 1 IFN-inducible transcripts and proteins in DM muscle with a similar phenomenon seen in blood [Greenberg, 2010a, 2010b; Lundberg and Helmers, 2010]. It is unknown what drives the sustained presence of type 1 IFN inducible molecules in myositis, but evidence that these molecules injure myofibers seems especially strong. Therapeutic development of IFNα blockade has been explored in a phase 1b trial of MEDI-545 (anti-IFNα antibody) in DM and PM [ClinicalTrials.gov identifier: NCT00004451]. The data has not yet been released.

### *Future potential biologic agents*

Understanding the pivotal mediators of inflammatory muscle disease at a molecular level will lead to even more targets for therapy. A study [Szodoray *et al.* 2010] sought to describe a broad spectrum of T- and B-cell cytokines, growth

factors, and chemokines in patients with IIMs realizing that there are characteristic differences in the different subtypes which could reflect their distinct pathophysiological pathways. A complex set of immune and inflammatory modulating cytokines were found to be significantly upregulated as compared with healthy controls, also distinguishing between IIM subsets. This can lead to future use as biomarkers of disease, as well as open avenues for potential novel therapeutic targets. CXCL10, a Th1 chemokine, has also been found to be a viable pharmacologic target [Crescioli *et al.* 2011].

## Stem-cell transplantation

### *Autologous stem-cell transplantation*

In severe refractory cases of myositis, autologous stem-cell transplantation (ASCT) may be a consideration. In one case reported [Henes *et al.* 2009], a patient with anti-SRP myositis treated unsuccessfully with multiple immunosuppressants including IVIG, high-dose cyclophosphamide, alemtuzumab and Infliximab, was successfully treated with myeloablative conditioning with cyclophosphamide. Following cyclophosphamide and total body irradiation with reinfusion of CD34+ autologous stem cells and granulocyte colony stimulating factor, a normalization of CK levels, increase in muscle strength, and absence of myositis on MRI was seen. This response was durable after 3 years of follow up. A case report of two patients with severe progressive JDM similarly showed dramatic improvements and sustained remission with ASCT [Holzer *et al.* 2010]. ASCT was performed using a CD3/CD19 depleted graft after immunoablative conditioning with fludarabine, cyclophosphamide, and antithymocyte globulin, which the authors concluded was a low toxicity therapeutic option for severe, refractory disease.

### *Mesenchymal stem-cell transplantation*

Mesenchymal stem cells can suppress the activity of various immune cells and have very limited immunogenicity. An open-label pilot study using allogeneic mesenchymal stem-cell transplantation (MSCT) was performed in 10 patients with drug-resistant DM/PM [Wang *et al.* 2011]. For most patients, serum CK decreased together with clinically meaningful improvements and tapering of drug intake. However, on follow up for about 1 year, none of the patients completely stopped their immunosuppressive therapy. This suggests that MSCT does not provide a cure, but may prove to be a useful adjunct in patients with poorly controlled disease. It should also be noted that two patients died following MSCT directly due to disease recurrence after infection.

## Gene therapy

In cases with dismal response to current treatment such as with IBM, a promising avenue for treatment has emerged with the use of molecular therapy. Although correction of the underlying defect would be ideal as has been attempted in limb-girdle muscular dystrophy [Mendell *et al.* 2009, 2010], an approach to increase muscle size and strength may be opportune in the idiopathic inflammatory myopathies whose genetic basis is not well known.

### *Follistatin*

Myostatin is a transforming growth factor β family member expressed in adult and developing skeletal muscle and is a negative regulator of muscle growth [Haidet *et al.* 2010]. Strategies to increase muscle size and strength through inhibition of the myostatin pathway have been encouraging [Rodino-Klapac *et al.* 2009]. The furthest along in development is the utilization of follistatin, which has emerged as a potent antagonist of myostatin with the ability to hinder access to signaling receptors on skeletal muscle. It was initially isolated in porcine ovarian follicular fluid and attenuates the release of follicle-stimulating hormone. Follistatin has multiple functions aside from its role in reproductive physiology that raises concern in its targeted approach for use in muscle diseases. A gene therapy approach to myostatin inhibition through follistatin has been explored as it offers the potential for a single administration of vector carrying the follistatin gene with persistent expression for many years, perhaps even for the lifetime of the individual. Preliminary studies using alternatively spliced cDNA of follistatin delivered by adeno-associated virus demonstrated increased muscle size and strength with reduced fibrosis in dystrophic mice [Haidet *et al.* 2008]. Preclinical studies performed on healthy monkeys showed similar results and was shown to be safe and effective [Kota *et al.* 2009]. Given this, using gene therapy with follistatin for inhibition of myostatin is well-positioned for use in the inflammatory myopathies. A follistatin gene therapy trial is currently underway in nine patients with IBM

conducted at Nationwide Children's Hospital in Ohio (The Myositis Association, personal communication, 2011).

### *Nuclear receptor corepressor 1*

Transcription coregulators control the activity of many transcription factors and have wide ranging effects on gene expression. A study demonstrated that the deletion of the muscle-specific nuclear receptor corepressor 1 (NCoR1) gene in mice led to enhanced exercise endurance due to increased muscle mass as well as mitochondrial number and activity [Yamamoto *et al.* 2011]. Although this data is preliminary, interference with corepressors such as NCoR1 may find use as strategies to improve muscle mass and function.

### *RNA interference*

RNA interference (RNAi) is a natural process that cells use to turn down the activity of specific genes. In conjunction with this, MiRNAs, or microRNAs, are endogenous triggers of RNAi which have been shown to have essential roles in developmental processes including in skeletal muscle [Sibley and Wood, 2011; Mishra and Bertino, 2009]. A key feature of the RNAi and miRNA mechanism is sequence specificity. A differential expression of MiRNAs has been described in several pathological processes including PM, DM, and IBM [Sibley and Wood, 2011]. Although the exact significance of this is unclear, therapies manipulating miRNA activity may be a particularly powerful strategy for targeting dysregulated disease pathways in the future.

## Other agents

### *Retinoids*

One study [Ohyanagi *et al.* 2009] examined the effect of retinoids on experimental autoimmune myositis. Retinoids have important roles in cell proliferation, differentiation, and morphogenesis with modulating function on inflammatory and immunocompetent cells including T cells and macrophages. Following induction of autoimmune myositis in mice, administration of AM80 (a synthetic retinoid launched in the Japanese market for promyelocytic leukemia) showed attenuated inflammatory changes both prophylactically and therapeutically. There was also an attenuated production of serum antimyosin antibodies found. This finding was thought to be due to regulation of Th differentiation, reduction of antimyosin antibody production, and decreased chemokine expression.

### *Calpeptin*

It has been hypothesized that calpain (a $Ca^{2+}$-sensitive protease) activation bridges between extracellular inflammatory stress and intracellular secondary inflammatory changes seen in muscle cells in IIMs. With the addition of calpeptin, a calpain inhibitor, to rat myoblast cells following extracellular inflammatory stimulation, there was attenuated apoptosis and expression of MHC-1 and inflammation related transcription factors demonstrated [Nozaki *et al.* 2011]. The authors propose that calpain may be a potential therapeutic target for the treatment of inflammatory myopathies.

### *Mizoribine*

Mizoribine is a purine antimetabolite that inhibits T-cell activation and proliferation as well as B-cell proliferation. It is approved in Japan for the inhibition of rejection after renal transplant, lupus nephritis, and RA. Successful use of Mizoribine as a steroid-sparing agent in a patient with PM that had developed CVA, DM and MI after steroid use was reported [Suwa *et al.* 2009].

### *Statins*

Statins have pleiotropic effects including the inhibition of inflammation and immunomodulatory and antioxidant effects. A pilot study explored the use of simvastatin 40 mg in IBM [Sancricca *et al.* 2011]. In an open-label trial in 14 patients over 12 months, none of the patients showed significant clinical improvement. Given the already known toxic effects in muscle, simvastatin cannot be recommended for the treatment of sporadic inclusion body myositis at this time.

## Exercise training

More recently, physical exercise in combination with immunosuppressive treatment has been found to have beneficial effects on clinical outcomes in patients with myositis [Nader and Lundberg, 2009]. Data is also suggestive that exercise exerts anti-inflammatory effects both systemically as well as locally in muscle. A new nonpharmacological approach has been proposed for IBM patients involving vascular occlusion in

association with resistance training [Gualano *et al.* 2010a, 2010b]. Investigators demonstrated that by restricting muscle blood flow using tourniquet cuffs in conjunction with moderate intensity resistance training, a gain in muscle mass and function was seen after a 12-week training program. A video component of the article can be found at http://www.jove.com/details.php?id=1894.

## Conclusion

In summary, the treatment of inflammatory myopathies to date has been complicated by the rarity of the disease and the paucity of large randomized clinical trials. With the introduction and use of the IMACS standardized response criteria (definition of improvement) in clinical trials, conduction of trials and comparison between them will be easier. Although challenges remain as to the treatment of refractory cases, continued elucidation of the pathogenesis, understanding of the different phenotypes, antibody status, cytokine milieu, and even regulatory genes has opened up a host of avenues for therapeutic targets. We anticipate that these efforts will eventually translate into better clinical outcomes for myositis patients.

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## Conflict of interest statement

The authors declare that Dr Christopher-Stine has served as a consultant for Medimmune.

## References

Bakewell, C.J. and Raghu, G. (2011) Polymyositis associated with severe interstitial lung disease: remission after three doses of IV immunoglobulin. *Chest* 139: 441–443.

Couderc, M., Gottenberg, J.E., Mariette, X., Hachulla, E., Sibilia, J., Fain, O., *et al.* (2011) Efficacy and safety of rituximab in the treatment of refractory inflammatory myopathies in adults: results from the AIR registry. *Rheumatology (Oxford, England)* 50: 2283–2289.

Crescioli, C., Sottili, M., Bonini, P., Cosmi, L., Chiarugi, P., Romagnani, P., *et al.* (2011) Inflammatory response in human skeletal muscle cells: CXCL10 as a potential therapeutic target. *Eur J Cell Biol* 91: 139–149.

Dalakas, M.C., Rakocevic, G., Schmidt, J., Salajegheh, M., McElroy, B., Harris-Love, M.O., *et al.* (2009) Effect of alemtuzumab (CAMPATH 1-H) in patients with inclusion-body myositis. *Brain* 132: 1536–1544.

Danieli, M.G., Pettinari, L., Moretti, R., Logullo, F. and Gabrielli, A. (2011) Subcutaneous immunoglobulin in polymyositis and dermatomyositis: a novel application. *Autoimmun Rev* 10: 144–149.

Diot, E., Carmier, D., Marquette, D., Marchand-Adam, S., Diot, P. and Lesire, V. (2011) IV immunoglobulin might be considered as a first-line treatment of severe interstitial lung disease associated with polymyositis. *Chest* 140: 562–563.

Donofrio, P.D., Berger, A., Brannagan, T.H.,III, Bromberg, M.B., Howard, J.F., Latov, N., *et al.* (2009) Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee. *Muscle Nerve* 40: 890–900.

Dorph, C., Dastmalchi, M., Alexanderson, H., Ottosson, C., Lindroos, E., Nennesmo, I. *et al.* (2009) Anakinra in patients with refractory idiopathic inflammatory myopathies. *Arthritis Rheum* 60(Suppl. 10): 589.

Frikha, F., Rigolet, A., Behin, A., Fautrel, B., Herson, S. and Benveniste, O. (2009) Efficacy of rituximab in refractory and relapsing myositis with anti-JO1 antibodies: a report of two cases. *Rheumatology (Oxford, England)* 48: 1166–1168.

Greenberg, S.A. (2010a) Dermatomyositis and type 1 interferons. *Curr Rheumatol Rep* 12: 198–203.

Greenberg, S.A. (2010b) Type 1 interferons and myositis. *Arthritis Res Ther* 12(Suppl. 1): S4.

Gualano, B., Neves, M., Jr, Lima, F.R., Pinto, A.L., Laurentino, G., Borges, C., *et al.* (2010a) Resistance training with vascular occlusion in inclusion body myositis: a case study. *Med Sci Sports Exercise* 42: 250–254.

Gualano, B., Ugrinowitsch, C., Neves, M., Jr, Lima, F.R., Pinto, A.L., Laurentino, G., *et al.* (2010b) Vascular occlusion training for inclusion body myositis: a novel therapeutic approach. *J Visual Exp* 40: 1894, DOI: 10.3791/1894.

Haidet, A.M., Rizo, L., Handy, C., Umapathi, P., Eagle, A., Shilling, C., *et al.* (2008) Long-term enhancement of skeletal muscle mass and strength by single gene administration of myostatin inhibitors. *Proc Natl Acad Sci USA* 105: 4318–4322.

Hak, A., De Paepe, B., De Bleecker, J., Tak, P. and De Visser, M. (2011) Dermatomyositis and polymyositis: new treatment targets on the horizon. *Netherlands J Med* 69: 410–421.

Haroon, M. and Devlin, J. (2010) Rituximab as a first-line agent for the treatment of dermatomyositis. *Rheumatol Int*: 1-2.

Hartung, H.P., Mouthon, L., Ahmed, R., Jordan, S., Laupland, K.B. and Jolles, S. (2009) Clinical applications of intravenous immunoglobulins (IVIg) - beyond immunodeficiencies and neurology. *Clin Exp Immunol* 158(Suppl. 1): 23–33.

Henes, J.C., Heinzelmann, F., Wacker, A., Seelig, H.P., Klein, R., Bornemann, A., *et al.* (2009) Antisignal recognition particle-positive polymyositis successfully treated with myeloablative autologous stem cell transplantation. *Ann Rheum Dis* 68: 447–448.

Holzer, U., van Royen-Kerkhof, A., van der Torre, P., Kuemmerle-Deschner, J., Well, C., Handgretinger, *et al.* (2010) Successful autologous stem cell transplantation in two patients with juvenile dermatomyositis. *Scand J Rheumatol* 39: 88–92.

Joshi, N., Nautiyal, A. and Davies, P.G. (2011) Successful use of rituximab in recalcitrant skin predominant dermatomyositis. *J Clin Rheumatol* 17: 111–112.

Katz, U., Shoenfeld, Y. and Zandman-Goddard, G. (2011) Update on intravenous immunoglobulins (IVIg) mechanisms of action and off-label use in autoimmune diseases. *Curr Pharmaceut Des* 17: 3166–3175.

Kota, J., Handy, C.R., Haidet, A.M., Montgomery, C.L., Eagle, A., Rodino-Klapac, L.R., *et al.* (2009) Follistatin gene delivery enhances muscle growth and strength in nonhuman primates. *Sci Translational Med* 1(6): 6ra15.

Levesque, M.C. (2009) Translational mini-review series on B cell-directed therapies: recent advances in B cell-directed biological therapies for autoimmune disorders. *Clin Exp Immunol* 157: 198-208.

Levy, D.M., Bingham, C.A., Kahn, P.J., Eichenfield, A.H. and Imundo, L.F. (2010) Favorable outcome of juvenile dermatomyositis treated without systemic corticosteroids. *J Pediatrics* 156: 302–307.

Linardaki, G., Cherouvim, E., Goni, G. and Boki, K.A. (2011) Intravenous immunoglobulin treatment for pregnancy-associated dermatomyositis. *Rheumatol Int* 31: 113–115.

Lundberg, I.E. and Helmers, S.B. (2010) The type I interferon system in idiopathic inflammatory myopathies. *Autoimmunity* 43: 239–243.

Mahler, E.A., Blom, M., Voermans, N.C., van Engelen, B.G., van Riel, P.L. and Vonk, M.C. (2011) Rituximab treatment in patients with refractory inflammatory myopathies. *Rheumatology (Oxford, England)* 50: 2206–2213.

Majmudar, S., Hall, H.A. and Zimmermann, B. (2009) Treatment of adult inflammatory myositis with rituximab: an emerging therapy for refractory patients. *J Clin Rheumatol* 15: 338–340.

Marie, I., Menard, J.F., Hatron, P.Y., Hachulla, E., Mouthon, L., Tiev, K., *et al.* (2010) Intravenous immunoglobulins for steroid-refractory esophageal involvement related to polymyositis and dermatomyositis: a series of 73 patients. *Arthritis Care Res* 62: 1748–1755.

Mendell, J.R., Rodino-Klapac, L.R., Rosales-Quintero, X., Kota, J., Coley, B.D., Galloway, G., *et al.* (2009) Limb-girdle muscular dystrophy type 2D gene therapy restores alpha-sarcoglycan and associated proteins. *Ann Neurol* 66: 290–297.

Mendell, J.R., Rodino- Klapac, L.R., Rosales, X.Q., Coley, B.D., Galloway, G., Lewis, S., *et al.* (2010) Sustained alpha-sarcoglycan gene expression after gene transfer in limb-girdle muscular dystrophy, type 2D. *Ann Neurol* 68: 629–638.

Mishra, P.J. and Bertino, J.R. (2009) MicroRNA polymorphisms: the future of pharmacogenomics, molecular epidemiology and individualized medicine. *Pharmacogenomics* 10: 399–416.

Muscle Study Group (2011) A randomized, pilot trial of etanercept in dermatomyositis. *Ann Neurol* 70: 427–436.

Musuruana, J.L. and Cavallasca, J.A. (2011) Abatacept for treatment of refractory polymyositis. *Joint Bone Spine Rev Rhumatisme* 78: 431–432.

Nader, G.A. and Lundberg, I.E. (2009) Exercise as an anti-inflammatory intervention to combat inflammatory diseases of muscle. *Curr Opin Rheumatol* 21: 599–603.

Narazaki, M., Hagihara, K., Shima, Y., Ogata, A., Kishimoto, T. and Tanaka, T. (2011) Therapeutic effect of tocilizumab on two patients with polymyositis. *Rheumatology (Oxford, England)* 50: 1344–1346.

Nozaki, K., Das, A., Ray, S.K. and Banik, N.L. (2011) Calpeptin attenuated apoptosis and intracellular inflammatory changes in muscle cells. *J Neurosci Res* 89: 536–543.

Oddis, C., Reed, A., Aggarwal, R., Ascherman, D., Barohn, R., Feldman, B., *et al.* (2010) Rituximab in the treatment of refractory adult and juvenile dermatomyositis (DM) and adult polymyositis (PM) - The RIM Study. In: *ACR/ARHP Scientific Meeting*, Atlanta, GA, 10 November 2010.

Ohyanagi, N., Ishido, M., Suzuki, F., Kaneko, K., Kubota, T., Miyasaka, N., *et al.* (2009) Retinoid ameliorates experimental autoimmune myositis, with modulation of Th cell differentiation and antibody production in vivo. *Arthritis Rheum* 60: 3118–3127.

Okiyama, N., Sugihara, T., Iwakura, Y., Yokozeki, H., Miyasaka, N. and Kohsaka, H. (2009) Therapeutic effects of interleukin-6 blockade in a murine model of polymyositis that does not require interleukin-17A. *Arthritis Rheum* 60: 2505–2512.

Quick, A. and Tandan, R. (2011) Mechanisms of action of intravenous immunoglobulin in inflammatory muscle disease. *Curr Rheumatol Rep* 13: 192–198.

Recher, M., Sahrbacher, U., Bremer, J., Arndt, B., Steiner, U. and Fontana, A. (2010) Treatment of inclusion body myositis: is low-dose intravenous immunoglobulin the solution? *Rheumatol Int* 32: 469–472.

Rezaei, N., Abolhassani, H., Aghamohammadi, A. and Ochs, H.D. (2011) Indications and safety of intravenous and subcutaneous immunoglobulin therapy. *Expert Rev Clin Immunol* 7: 301–316.

Rodino-Klapac, L.R., Haidet, A.M., Kota, J., Handy, C., Kaspar, B.K. and Mendell, J.R. (2009) Inhibition of myostatin with emphasis on follistatin as a therapy for muscle disease. *Muscle Nerve* 39: 283–296.

Sancricca, C., Mora, M., Ricci, E., Tonali, P.A., Mantegazza, R. and Mirabella, M. (2011) Pilot trial of simvastatin in the treatment of sporadic inclusion-body myositis. *Neurological Sci* 32: 841–847.

Sem, M., Molberg, O., Lund, M.B. and Gran, J.T. (2009) Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. *Rheumatology (Oxford, England)* 48: 968–971.

Sibley, C.R. and Wood, M.J. (2011) The miRNA pathway in neurological and skeletal muscle disease: implications for pathogenesis and therapy. *J Mol Med (Berlin, Germany)* 89: 1065–1077.

Stubgen, J.P. (2011) Tumor necrosis factor-alpha as a potential therapeutic target in idiopathic inflammatory myopathies. *J Neurol* 258: 961–970.

Suwa, A., Hirakata, M., Kaneko, Y., Sato, S., Suzuki, Y. and Kuwana, M. (2009) Successful treatment of refractory polymyositis with the immunosuppressant mizoribine: case report. *Clin Rheumatol* 28: 227–229.

Szodoray, P., Alex, P., Knowlton, N., Dozmorov, I., Csipo, I., Nagy, A.T., *et al.* (2010) Idiopathic inflammatory myopathies, signified by distinctive peripheral cytokines, chemokines and the TNF family members B-cell activating factor and a proliferation inducing ligand. *Rheumatology (Oxford, England)* 49: 1867–1877.

Valiyil, R., Casciola-Rosen, L., Hong, G., Mammen, A. and Christopher-Stine, L. (2010) Rituximab therapy for myopathy associated with anti-signal recognition particle antibodies: a case series. *Arthritis Care Res* 62: 1328–1334.

Vandenbroucke, E., Grutters, J.C., Altenburg, J., Boersma, W.G., ter Borg, E.J. and van den Bosch, J.M. (2009) Rituximab in life threatening antisynthetase syndrome. *Rheumatol Int* 29: 1499–1502.

Wang, D., Zhang, H., Cao, M., Tang, Y., Liang, J., Feng, X., *et al.* (2011) Efficacy of allogeneic mesenchymal stem cell transplantation in patients with drug-resistant polymyositis and dermatomyositis. *Ann Rheum Dis* 70: 1285–1288.

Whelan, B.R. and Isenberg, D.A. (2009) Poor response of anti-SRP-positive idiopathic immune myositis to B-cell depletion. *Rheumatology (Oxford, England)* 48: 594–595.

Yamamoto, H., Williams, E.G., Mouchiroud, L., Canto, C., Fan, W., Downes, M., *et al.* (2011) NCoR1 is a conserved physiological modulator of muscle mass and oxidative function. *Cell* 147: 827–839.

Zong, M., Malmstrom, V. and Lundberg, I.E. (2011) Anakinra effects on T cells in patients with refractory idiopathic inflammatory myopathies. *Ann Rheum Dis* 70(Suppl. 2): 80–81.