HHS Public Access

Author manuscript

Curr Treatm Opt Rheumatol. Author manuscript; available in PMC 2022 June 01.

Published in final edited form as:

Curr Treatm Opt Rheumatol. 2021 June ; 7(2): 150–160. doi:10.1007/s40674-021-00174-1.

Therapeutic management of immune-mediated necrotizing myositis

Emma Weeding[1], **Eleni Tiniakou**[1]

[1]Department of Medicine, Division of Rheumatology, Mason Lord, Center Tower, Johns Hopkins University School of Medicine, 5200 Eastern Avenue, Baltimore, MD, 21224, USA

Abstract

Purpose of Review: The idiopathic inflammatory myopathies are a heterogeneous group of autoimmune disorders characterized by skeletal muscle inflammation leading to chronic muscle weakness. Immune-mediated necrotizing myopathy (IMNM) is a distinct subgroup of inflammatory myopathy typically characterized by myofiber necrosis with minimal inflammatory infiltrates on muscle biopsy, highly elevated creatine kinase levels, and infrequent extra-muscular involvement. This review provides an overview of currently recommended treatment strategies for IMNM, including discussion of disease activity monitoring and recommended first-line immunomodulatory agents depending on clinical phenotype and autoantibody status.

Recent Findings: IMNM can be divided into three subtypes based on autoantibody positivity: anti-3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) IMNM, anti-signal recognition particle (SRP) IMNM, and antibody negative IMNM. Autoantibody status in IMNM has considerable correlation with clinical phenotype, prognosis, and recommended choice of immunosuppressive agent. Patients with anti-HMGCR IMNM tend to respond well to intravenous immunoglobulin (IVIG), and IVIG monotherapy may be sufficient treatment for certain patients. In anti-SRP IMNM, early rituximab is commonly favored. More generally, prompt initiation of aggressive immunosuppression is often indicated, as both anti-SRP and anti-HMGCR IMNM can potentially cause debilitating weakness, and muscle atrophy and irreversible fatty replacement happen early in the disease course. Patients with IMNM frequently require combination therapy to achieve disease control, and have a high rate of relapse when tapering immunosuppression. Young age of onset is a poor prognostic factor.

Corresponding author: Eleni Tiniakou, etiniak1@jhmi.edu.

Authors' contributions: ET and EW participated in literature review as well as drafting and critical revision of the manuscript.

DECLARATIONS

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Emma Weeding and Eleni Tiniakou declare that they have no conflict of interest

Summary: IMNM can be severely disabling and often requires aggressive immunosuppression. For any given patient, the treatment strategy should be informed by the severity of their presenting features and autoantibody status. While our ability to treat IMNM has certainly improved, there remains a need for more prospective trials to inform optimal treatment strategies.

Keywords

HMGCR; Idiopathic inflammatory myopathies; Immunosuppression; Necrotizing myositis; Signal recognition particle; Treatment

INTRODUCTION

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune disorders characterized by chronic muscle weakness and skeletal muscle inflammation. Immune-mediated necrotizing myopathy (IMNM) is a distinct subgroup of IIM classically characterized by predominant myofiber necrosis with minimal inflammatory infiltrates on muscle biopsy(1). IMNM is also distinguished from other categories of IIM by highly elevated creatine kinase (CK) levels, paucity of extra-muscular involvement, and, occasionally, more severe disease that is difficult to fully control with immunosuppressive therapy(2). IMNM can be classified based either on proposed European Neuromuscular Centre (ENMC) criteria(3) or, in routine practice, the detection of characteristic myositis-associated autoantibodies in the appropriate clinical context. Indeed, the most recent ENMC criteria divide IMNM into three subtypes based on autoantibody positivity: anti-3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) IMNM, anti-signal recognition particle (SRP) IMNM, and antibody negative IMNM(4). IMNM can also occur in association with malignancy or other connective tissue disorders such as scleroderma(5,6). The focus of this review will be on the three primary subtypes of IMNM based on autoantibody positivity, though the general treatment principles discussed herein also apply to patients who have an overlap syndrome with associated necrotizing myositis.

While it is likewise outside the scope of this review to discuss the presentation and diagnosis of IMNM in detail, it is important to understand certain clinical features as they relate to guiding therapeutic decisions. Autoantibody status in IMNM has considerable correlation with clinical phenotype, prognosis, and recommended choice of immunosuppressive therapy. We will thus briefly describe these typical autoantibody phenotypes and, later, detail treatment of IMNM in relation to autoantibody status.

The first reports of what is now known as anti-HMGCR IMNM described a necrotizing myositis associated with statin usage that, in comparison to the more common drug-induced toxic myopathy, did not improve after statin discontinuation and in fact required aggressive immunosuppression to treat(7,8). The anti-HMGCR antibody was later identified(9,10). We now also appreciate that roughly one third of North American patients with anti-HMGCR IMNM do not have any statin exposure(10). Those who are statin-naïve tend to be younger, have higher CK levels, are more likely to be Asian, and at the same time, younger patients may be less responsive to treatment(11–14). Anti-HMGCR IMNM generally affects men and women roughly equally, though some studies have shown a female predominance(15).

Anti-SRP IMNM is one of the most severe inflammatory myopathies, and tends to cause rapidly progressive weakness with markedly elevated CK(16–20). Women are affected more often than men(21,22). Dysphagia is present in roughly half of patients at the time of diagnosis(16,19,20) and muscle damage is more intense(23) compared to those with anti-HMGCR.

Compared to the other two autoantibody groups, seronegative IMNM remains poorly described. Indeed, this subgroup of IMNM may represent its own heterogeneous subfamily of disorders associated with hitherto unidentified autoantibodies and/or other unknown precipitants of disease. The most notable unifying feature of this group is a markedly increased risk of synchronous malignancy(5) which is discussed in greater detail below.

MEDICATION MANAGEMENT

Goals of Treatment

General goals of treatment in IMNM (and IIM overall) include maximizing strength and functional status, normalizing creatine kinase (CK), and minimizing medication side effects. While the ideal scenario is for a patient to achieve fully normal strength, this may not be possible depending on how much irreversible fatty replacement of muscle has already occurred prior to starting immunosuppressive medication. We thus aim for complete suppression of appreciable muscle inflammation in order to prevent further damage and to help patients regain as much strength as possible.

It follows that strength needs to be clinically reassessed periodically. Manual muscle testing (MMT) remains the standard in this respect, as it is simple and quick to perform at clinical visits(24). It is not without limitations, however. MMT has been associated with a ceiling effect in patients with high baseline strength and/or only mild weakness(25,26). It also lacks the ability to assess other aspects of muscle function, like endurance. In comparison, the myositis Functional Index-2 (FI2) examines muscle endurance by asking patients to repeat certain movements to the beat of a metronome(25). The FI2 correlates with functional status, changes in response to treatment, and does not have the ceiling effect seen with MMT(25–28). In our cohort, we found that the FI2 can identify deficits that MMT does not. Specifically, FI2 correlated with MMT and inversely with CK, but was highly variable and often abnormal in patients with normal strength by MMT(29). The FI2 is time consuming and thus difficult to apply routinely in clinical practice, but does highlight the need for caution when interpreting otherwise “normal” manual strength testing in a patient who remains symptomatic, functionally limited, or with serological or imaging evidence of active muscle inflammation.

In parallel to physical exam, muscle inflammation should also be assessed by following muscle enzymes such as CK and aldolase. We generally aim for a CK within normal limits, as indicated by the performing lab, for a patient to be considered in remission, as an elevated CK commonly indicates active disease even in the context of normal muscle strength. In such cases, muscle MRI can be useful in revealing the presence and extent of muscle involvement. Nevertheless, the optimal treatment approach in these situations is not known –that is, it is not clear if it is better to monitor a patient on their existing regimen (at the

risk of allowing further muscle damage) or to add immunosuppression (increasing the risk of infection and medication side effects). Given the lack of clinical evidence to support one strategy over the other, this decision should be based on a discussion with the patient regarding the risks and benefits of a more aggressive approach and should take into account individual factors such as the patient's age, activity level, infection risk, etc.

General Approach to Treatment

Immunomodulation is the cornerstone of treatment in IMNM, as with IIM in general (excluding inclusion body myositis). At the time of diagnosis, corticosteroids are often the first agent given due to their rapid and broad overall efficacy in IIM(4,30,31). A dose of 1 mg/kg/day of prednisone (or equivalent) is a typical starting dose, though pulsed methylprednisolone can be considered in patients with severe or rapidly progressive weakness, dysphagia, respiratory failure, or other severe organ damage. While not a standard practice, one could avoid steroids depending the severity of the presenting symptoms, and initiate the steroid sparing regimen instead or utilize IVIG as a fast-acting agent (32–34), thus sparing the patient from the unnecessary side effects of steroids.

All patients with IMNM should additionally be started on a steroid-sparing agent up front. There are unfortunately no clinical trials to guide the selection of immunosuppressive agent in IMNM and thus treatment has historically been guided by observational studies and expert opinion. Treatment guidelines suggested by an ENMC working group(4) propose a combination of corticosteroids and methotrexate as appropriate first-line therapy for IMNM in general. For patients with anti-HMGCR IMNM, the addition of intravenous immunoglobulin (IVIG) instead of or in addition to methotrexate is recommended. Similarly, for those with anti-SRP disease, the use of rituximab instead of or in addition to methotrexate is encouraged. Indeed, initial choice of immunosuppressive drug(s) should be heavily informed by autoantibody status and overall severity of disease and these phenotypic considerations will be discussed shortly.

IMNM can be disabling and difficult to treat. Within our cohort, only half of patients with anti-SRP IMNM achieved normal or near-normal strength even after four years of treatment, with similar results in anti-HMGCR patients after two years(14,35). Young age of onset is a poor prognostic factor(14,17,35) and we often recommend aggressive combination therapy for such individuals. Steroid monotherapy should be avoided in any patient with IMNM as this is usually not sufficient to adequately control disease activity or prevent further damage. Muscle atrophy and irreversible fatty replacement happen early in IIM, including IMNM, as demonstrated by Pinal-Fernandez *et al.* in a retrospective review of thigh MRIs in nearly 700 participants with various types of IIM(23). Those with IMNM had more diffuse muscle atrophy, edema, and fatty replacement independent of disease duration compared to those with dermatomyositis or polymyositis. Participants with anti-SRP antibodies were significantly more likely to have muscle atrophy and/or fatty replacement compared to those with anti-HMGCR disease as well. In a retrospective study by Meyer *et al.*(34), delay in initiation of immunosuppressive treatment correlated with more recalcitrant disease in patients with anti-HMCR IMNM (OR 0.92, 95% CI 0.85–0.97).

Approach to Treatment Based on Autoantibody

Anti-HMGCR—Patients with anti-HMGCR IMNM tend to respond well to IVIG, sometimes exquisitely so. IVIG monotherapy, even without steroids, may in fact be sufficient treatment for certain anti-HMGCR patients. In one case series, three patients with statin-associated anti-HMGCR disease who declined steroids (due to comorbidities) received IVIG dosed at 2 g/kg monthly as monotherapy(32). All three experienced marked improvements in CK after 2–3 cycles of IVIG, and two became completely asymptomatic with normal strength. In a different retrospective study of IMNM, including anti-HMGCR IMNM, introduction of IVIG within three months of diagnosis was associated with a higher likelihood of marked improvement in strength at six months, though this effect was not sustained on longer term follow-up(6).

Reintroduction (or initiation) of statins should be avoided in anyone with anti-HMGCR IMNM as this may lead to disease flares(36,37). This creates a significant therapeutic challenge in patients with hyperlipidemia or other cardiovascular risk factors which would normally warrant statin usage. Ezetimibe can rarely cause a toxic myopathy(38) and we recommend it be used only with considerable caution (e.g. using a starting dose of once weekly rather than once daily) and with a low threshold for discontinuation if a patient exhibits worsening muscle disease. A more promising alternative are the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which preliminarily appear to be safe and possibly even beneficial in IMNM. In a retrospective study, we identified eight patients with anti-HMGCR IMNM in our cohort who were receiving PCSK9 inhibitors for hyperlipidemia(39). While on these medications (in addition to immunosuppressive therapy), none of these patients developed worsening muscle strength or progressively worsened muscle enzymes over an average follow-up period of 18 months. Interestingly, two participants experienced a marked clinical improvement after starting PCSK9 inhibitors such that their immunosuppressive therapy could be tapered considerably. Certainly more data is needed to explain this unexpected finding, but a possible mechanistic explanation is that PCSK9 inhibitors may actually modulate disease activity by lowering HMGCR levels(40,41).(35)

Anti-SRP—Early rituximab is often favored in anti-SRP disease, and this approach is included in ENMC guidelines(4). Valiyil *et al.* reported the largest early case series of such, where six out of eight patients with refractory anti-SRP disease demonstrated a significant and sustained response to rituximab(42). For some of these patients, the positive effects were dramatic –several were initially wheelchair- or bed-bound or critically ill despite aggressive immunosuppression with multiple other agents (including cyclophosphamide), but were able to regain the ability to ambulate or otherwise become increasingly independent in their activities with rituximab. A larger longitudinal study from Pinal-Fernandez *et al.* re-demonstrated these benefits(35). Of 17 anti-SRP patients treated with rituximab, 13 experienced significant clinical improvement. The benefit of an initial course of rituximab was maintained for over two years in certain patients, though the overall response was variable, with others requiring intermittent or regular retreatment.

Combination Therapy and Other Agents

Patients with IMNM frequently require combination therapy to achieve disease control and have a high relapse rate when tapering immunosuppression(6,8,14,15,17,19). It is thus often necessary to add additional immunosuppressive agents to the recommended first- or second-line drugs discussed above. Other medications used in IMNM have included azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine, and cyclophosphamide, though evidence in picking one agent over the other remains limited(4). As in other rheumatologic diseases, response to therapy can be idiosyncratic and difficult to predict, so a given patient may require multiple trials of different medications and combinations. For instance, Maeshima *et al.* reported on one patient with anti-SRP IMNM who achieved remission on abatacept (which is rarely used for myositis) after failing numerous other immunosuppressive agents, though not including rituximab as per current practice(43).High-dose cyclophosphamide (HiCy) may be an effective treatment option for refractory cases of IMNM. In a retrospective study from our Myositis Center, Mecoli *et al.* identified five patients (three with anti-SRP and two with anti-HMGCR antibodies) with severe refractory IMNM who were given HiCy treatment without stem cell rescue(44). Two of these patients experienced dramatically improved strength and muscle enzymes such that they were weaned off of immunosuppression and remained in remission for >30 months each by the time of chart review. Both of these individuals were anti-SRP positive. Cyclophosphamide is of course not without significant risk. In this study, all but one of the patients developed febrile neutropenia, but fortunately all recovered.

Plasmapheresis has been used in IMNM, though published data on its efficacy is very limited(45). In 2006, Arlet *et al.* reported dramatic improvement in two patients with anti-SRP disease who were treated with steroids and plasmapheresis followed by rituximab(46). However, in retrospect, it is difficult to comment on the contribution of plasmapheresis in this scenario, given the now known efficacy of rituximab in anti-SRP IMNM. Plasmapheresis monotherapy was not effective for corticosteroid-resistant dermatomyositis or polymyositis in one randomized controlled trial(47).

Adjunctive Approaches

Physical therapy is an important component in treating IIM, including IMNM. Historical concerns that strenuous physical activity may worsen muscle damage have, fortunately, turned out to be unfounded. Several clinical trials of exercise programs have shown that moderate aerobic exercise and/or strength training are not only safe in IIM, but also help maintain or improve muscle strength, aerobic fitness, and functional measures(48,49). Similarly, patients with dysphagia should be evaluated by a speech-language pathologist to learn safe swallowing maneuvers and, if needed, dietary modifications while awaiting the effect of immunosuppressive treatment.

Regardless of dysphagia, we recommend avoiding foods containing natural HMGCR inhibitors such as shiitake mushrooms(50), pu’er tea(51), and red yeast rice (which contains monacolin K, a substance chemically identical to lovastatin)(52) due to a theoretical concern that these agents might worsen necrotizing myositis. A clear causative link between these agents and myositis has not been definitively established, though from an epidemiological

perspective, it is interesting to note that statin-naïve anti-HMGCR IMNM is more common in East Asia, where these substances are consumed much more commonly compared to North America and Europe(12,13).

Surveillance Strategies

The association between IMNM and malignancy varies by autoantibody group. Anti-SRP IMNM has consistently not been found to associate with cancer(5,19,20,35). Conversely, nearly 30% of autoantibody negative IMNM cases were diagnosed with cancer (with standardized incidence ratio of 8.4) in one observational study, and three quarters of these cases occurred within three years of myositis diagnosis(5). Data for anti-HMGCR IMNM are mixed. The prevalence of cancer varies from 4–36% depending on cohort and the methods used for patient inclusion(5,20,37,53,54). There are no evidence-based guidelines to direct cancer screening in IMNM or in IIM overall. That said, in our center, we generally recommend at least a one-time CT scan of the chest, abdomen, and pelvis in addition to age-appropriate cancer screening, e.g. colonoscopy, mammograms.

In contrast to dermatomyositis or anti-synthetase syndrome, extra-muscular involvement is rare in IMNM. Indeed, the presence of significant lung, skin, or joint involvement should prompt one to seek an alternative diagnosis. Interstitial lung disease can be found in 10–25% of anti-SRP disease(19,35,55) and <5% of anti-HMGCR disease(14), but is usually mild if not entirely asymptomatic. We recommend PFTs be performed once around the time of diagnosis, but these do not necessarily need to be repeated unless the patient develops respiratory symptoms. The one important exception with respect to extra-muscular involvement in IMNM is cardiac involvement in anti-SRP IMNM. This is likewise relatively uncommon (no more than 20% in most cohorts) and generally manifests as arrhythmias or non-specific EKG abnormalities(17–19,55), but can rarely cause myocarditis and/or congestive heart failure potentially mandating high-dose steroids(16,56). Abnormalities on EKG or echocardiogram may be particularly common in younger patients –in one study, such abnormalities were found in 50% of participants with juvenile anti-SRP disease(57). We do not routinely screen patients for heart disease unless they are symptomatic, in which case a referral to a cardiologist is often recommended.

CONCLUSIONS

IMNM is a distinct subgroup of idiopathic inflammatory myopathy that can be severely disabling and often requires aggressive immunosuppression. For any given patient, the treatment strategy including first-line choice of immunosuppressive agent(s) should be informed by the severity of their presenting features, age of onset (with young age being a poor prognostic factor), and autoantibody status. Monitoring of disease activity should include serial assessment of muscle function and muscle enzymes, and treatment decisions should also be informed by a patient's reported symptoms and, as needed, advanced imaging such as MRI. While our ability to treat IMNM has certainly improved since this entity was first described, there remains a need for more prospective trials to best inform optimal treatment strategies.

Acknowledgements:

ET was funded through the Jerome L. Greene Foundation and Buck Foundation. EW was funded through the National Institutes of Arthritis, Musculoskeletal, and Skin Diseases (NIAMS) of the National Institutes of Health (NIH) under award number T32AR048522. This content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or NIAMS.

Funding: ET was funded through the Jerome L. Greene Foundation and Buck Foundation. EW was funded through the National Institutes of Arthritis, Musculoskeletal, and Skin Diseases (NIAMS) of the National Institutes of Health (NIH) under award number T32-AR048522. This content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or NIAMS.

REFERENCES

1. Amato AA, Greenberg SA. Inflammatory Myopathies: CONTINUUM: Lifelong Learning in Neurology. 201312;19:1615–33. [PubMed: 24305450]
2. Dalakas MC. Inflammatory Muscle Diseases. Longo DL, editor. New England Journal of Medicine. 2015430;372(18):1734–47.
3. De Bleecker JL, De Paepe B, Aronica E, de Visser M, Amato A, Aronica E, et al.205th ENMC International Workshop: Pathology diagnosis of idiopathic inflammatory myopathies Part II 28–30 March 2014, Naarden, The Netherlands. Neuromuscular Disorders. 20153;25(3):268–72. [PubMed: 25572016]
4. Allenbach Y, Mammen AL, Benveniste O, Stenzel W, Immune-Mediated Necrotizing Myopathies Working Group. 224th ENMC International Workshop:: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14–16 October 2016. Neuromuscul Disord. 2018;28(1):87–99. [PubMed: 29221629] ** This study includes the recommendation of the IMNM Working Group regarding definition, diagnosis and possible treatment of IMNM based on expert opinion and review of current literature.
5. Allenbach Y, Keraen J, Bouvier A- M, Jooste V, Champtiaux N, Hervier B, et al.High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. Brain. 2016;139(Pt 8):2131–5. [PubMed: 27086869]
6. Kassardjian CD, Lennon VA, Alfugham NB, Mahler M, Milone M. Clinical Features and Treatment Outcomes of Necrotizing Autoimmune Myopathy. JAMA Neurol. 20159;72(9):996–1003. [PubMed: 26192196]
7. Needham M, Fabian V, Knezevic W, Panegyres P, Zilko P, Mastaglia FL. Progressive myopathy with up-regulation of MHC-I associated with statin therapy. Neuromuscul Disord. 20072;17(2):194–200. [PubMed: 17241784]
8. Grable-Esposito P, Katzberg HD, Greenberg SA, Srinivasan J, Katz J, Amato AA. Immune-mediated necrotizing myopathy associated with statins. Muscle Nerve. 20102;41(2):185–90. [PubMed: 19813188]
9. Christopher-Stine L, Casciola-Rosen LA, Hong G, Chung T, Corse AM, Mammen AL. A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. Arthritis Rheum. 20109;62(9):2757–66. [PubMed: 20496415]
10. Mammen AL, Chung T, Christopher-Stine L, Rosen P, Rosen A, Doering KR, et al.Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum. 20113;63(3):713–21. [PubMed: 21360500]
11. Werner JL, Christopher-Stine L, Ghazarian SR, Pak KS, Kus JE, Daya NR, et al.Antibody levels correlate with creatine kinase levels and strength in anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. Arthritis Rheum. 201212;64(12):4087–93. [PubMed: 22933019]
12. Ge Y, Lu X, Peng Q, Shu X, Wang G. Clinical Characteristics of Anti-3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Antibodies in Chinese Patients with Idiopathic Inflammatory Myopathies. PLoS ONE. 2015;10(10):e0141616.
13. Watanabe Y, Suzuki S, Nishimura H, Murata K, Kurashige T, Ikawa M, et al.Statins and myotoxic effects associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase autoantibodies: an observational study in Japan. Medicine (Baltimore). 20151;94(4):e416. [PubMed: 25634171]

14. Tiniakou E, Pinal-Fernandez I, Lloyd TE, Albayda J, Paik J, Werner JL, et al.More severe disease and slower recovery in younger patients with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. Rheumatology (Oxford). 201701;56(5):787–94. [PubMed: 28096458]
15. Allenbach Y, Drouot L, Rigolet A, Charuel JL, Jouen F, Romero NB, et al.Anti-HMGCR autoantibodies in European patients with autoimmune necrotizing myopathies: inconstant exposure to statin. Medicine (Baltimore). 20145;93(3):150–7. [PubMed: 24797170]
16. Targoff IN, Johnson AE, Miller FW. Antibody to signal recognition particle in polymyositis. Arthritis & Rheumatism. 199091;33(9):1361–70. [PubMed: 2403400]
17. Miller T, Al-Lozi MT, Lopate G, Pestronk A. Myopathy with antibodies to the signal recognition particle: clinical and pathological features. J Neurol Neurosurg Psychiatry. 200210;73(4):420–8. [PubMed: 12235311]
18. Kao AH, Lacomis D, Lucas M, Fertig N, Oddis CV. Anti-signal recognition particle autoantibody in patients with and patients without idiopathic inflammatory myopathy. Arthritis Rheum. 20041;50(1):209–15. [PubMed: 14730618]
19. Suzuki S, Nishikawa A, Kuwana M, Nishimura H, Watanabe Y, Nakahara J, et al.Inflammatory myopathy with anti-signal recognition particle antibodies: case series of 100 patients. Orphanet J Rare Dis. 2015513;10:61. [PubMed: 25963141]
20. Watanabe Y, Uruha A, Suzuki S, Nakahara J, Hamanaka K, Takayama K, et al.Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. J Neurol Neurosurg Psychiatry. 2016;87(10):1038–44. [PubMed: 27147697]
21. Quinn C, Salameh JS, Smith T, Souayah N. Necrotizing myopathies: an update. J Clin Neuromuscul Dis. 2015Mar;16(3):131–40.
22. Pinal-Fernandez I, Mammen AL. Spectrum of immune-mediated necrotizing myopathies and their treatments. Curr Opin Rheumatol. 2016Nov;28(6):619–24.
23. Pinal-Fernandez I, Casal-Dominguez M, Carrino JA, Lahouti AH, Basharat P, Albayda J, et al.Thigh muscle MRI in immune-mediated necrotising myopathy: extensive oedema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity. Ann Rheum Dis. 2017;76(4):681–7. [PubMed: 27651398]
24. Miller FW, Rider LG, Chung YL, Cooper R, Danko K, Farewell V, et al.Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. Rheumatology (Oxford). 200111;40(11):1262–73. [PubMed: 11709610]
25. Alexanderson H, Broman L, Tollbäck A, Josefson A, Lundberg IE, Stenström CH. Functional index-2: Validity and reliability of a disease-specific measure of impairment in patients with polymyositis and dermatomyositis. Arthritis Rheum. 2006215;55(1):114–22. [PubMed: 16463422]
26. Alexanderson H, Regardt M, Ottosson C, Alemo Munters L, Dastmalchi M, Dani L, et al.Muscle Strength and Muscle Endurance During the First Year of Treatment of Polymyositis and Dermatomyositis: A Prospective Study. J Rheumatol. 2018;45(4):538–46. [PubMed: 29419464]
27. Alexanderson H, Dastmalchi M, Esbjörnsson-Liljedahl M, Opava CH, Lundberg IE. Benefits of intensive resistance training in patients with chronic polymyositis or dermatomyositis. Arthritis & Rheumatism. 2007615;57(5):768–77. [PubMed: 17530676]
28. Hanaoka BY, Cleary LC, Long DE, Srinivas A, Jenkins KA, Bush HM, et al.Physical impairment in patients with idiopathic inflammatory myopathies is associated with the American College of Rheumatology functional status measure. Clinical Rheumatology. 201511;34(11):1929–37. [PubMed: 25388646]
29. Amici DR, Pinal-Fernandez I, Pagkatipunan R, Mears A, De Lorenzo R, Tiniakou E, et al.Muscle endurance deficits in myositis patients despite normal manual muscle testing scores. Muscle Nerve. 2018720; * This study demonstrates the limitations of the MMT in patients with normal or near normal muscle strength.
30. Dimachkie MM, Barohn RJ, Amato AA. Idiopathic inflammatory myopathies. Neurol Clin. 2014Aug;32(3):595–628, vii.
31. Mammen AAutoimmune muscle disease. Handb Clin Neurol. 2016;133:467–84. [PubMed: 27112692]

32. Mammen AL, Tiniakou E. Intravenous Immune Globulin for Statin-Triggered Autoimmune Myopathy. N Engl J Med. 20151022;373(17):1680–2. [PubMed: 26488714]
33. Aggarwal R, Moghadam-Kia S, Lacomis D, Malik A, Qi Z, Koontz D, et al.Anti-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibody in necrotizing myopathy: treatment outcomes, cancer risk, and role of autoantibody level. Scand J Rheumatol. 2019125;1–7.
34. Meyer A, Troyanov Y, Drouin J, Oligny-Longpré G, Landon-Cardinal O, Hoa S, et al.Statin-induced anti-HMGCR myopathy: successful therapeutic strategies for corticosteroid-free remission in 55 patients. Arthritis Res Ther. 202018;22(1):5. [PubMed: 31915059] ** This retrospective study demonstrated the importance of avoiding delays in treatment in order to achieve disease remission.
35. Pinal-Fernandez I, Parks C, Werner JL, Albayda J, Paik J, Danoff SK, et al.Longitudinal Course of Disease in a Large Cohort of Myositis Patients With Autoantibodies Recognizing the Signal Recognition Particle. Arthritis Care Res (Hoboken). 2017;69(2):263–70. [PubMed: 27111848]
36. Mammen AL. Statin-Associated Autoimmune Myopathy. N Engl J Med. 2016218;374(7):664–9. [PubMed: 26886523]
37. Tiniakou E, Christopher-Stine L. Immune-mediated necrotizing myopathy associated with statins: history and recent developments. Curr Opin Rheumatol. 2017Nov;29(6):604–11.
38. Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Canadian Journal of Cardiology. 2006;22(2):141–4.
39. Tiniakou E, Rivera E, Mammen AL, Christopher-Stine L. Use of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors in Statin-Associated Immune-Mediated Necrotizing Myopathy: A Case Series. Arthritis Rheumatol. 2019;71(10):1723–6. [PubMed: 31058470] ** This case-series exhibited the safety of PCSK9 inhibitors as cholesterol-lowering treatment strategy in patients with anti-HMGCR IMNM.
40. Lan H, Pang L, Smith MM, Levitan D, Ding W, Liu L, et al.Proprotein convertase subtilisin/kexin type 9 (PCSK9) affects gene expression pathways beyond cholesterol metabolism in liver cells. J Cell Physiol. 20107;224(1):273–81. [PubMed: 20333646]
41. Zhang L, McCabe T, Condra JH, Ni YG, Peterson LB, Wang W, et al.An anti-PCSK9 antibody reduces LDL-cholesterol on top of a statin and suppresses hepatocyte SREBP-regulated genes. Int J Biol Sci. 2012;8(3):310–27. [PubMed: 22355267]
42. Valiyil R, Casciola-Rosen L, Hong G, Mammen A, Christopher-Stine L. Rituximab therapy for myopathy associated with anti-signal recognition particle antibodies: a case series. Arthritis Care Res (Hoboken). 20109;62(9):1328–34. [PubMed: 20506493]
43. Maeshima K, Kiyonaga Y, Imada C, Iwakura M, Hamasaki H, Haranaka M, et al.Successful treatment of refractory anti-signal recognition particle myopathy using abatacept. Rheumatology (Oxford). 20142;53(2):379–80. [PubMed: 23920268]
44. Mecoli CA, Lahouti AH, Brodsky RA, Mammen AL, Christopher-Stine L. High-dose cyclophosphamide without stem cell rescue in immune-mediated necrotizing myopathies. Neurol Neuroimmunol Neuroinflamm. 2017;4(5):e381. [PubMed: 28975138]
45. Ramanathan S, Langguth D, Hardy TA, Garg N, Bundell C, Rojana-Udomsart A, et al.Clinical course and treatment of anti-HMGCR antibody-associated necrotizing autoimmune myopathy. Neurol Neuroimmunol Neuroinflamm. 20156;2(3):e96.
46. Arlet J- B, Dimitri D, Pagnoux C, Boyer O, Maisonobe T, Authier F- J, et al.Marked efficacy of a therapeutic strategy associating prednisone and plasma exchange followed by rituximab in two patients with refractory myopathy associated with antibodies to the signal recognition particle (SRP). Neuromuscul Disord. 20065;16(5):334–6. [PubMed: 16616848]
47. Miller FW, Leitman SF, Cronin ME, Hicks JE, Leff RL, Wesley R, et al.Controlled Trial of Plasma Exchange and Leukapheresis in Polymyositis and Dermatomyositis. New England Journal of Medicine. 1992521;326(21):1380–4.
48. Habers GEA, Takken T. Safety and efficacy of exercise training in patients with an idiopathic inflammatory myopathy—a systematic review. Rheumatology. 201111;50(11):2113–24. [PubMed: 21890619]

49. Alemo Munters L, Dastmalchi M, Andgren V, Emilson C, Bergegård J, Regardt M, et al.Improvement in health and possible reduction in disease activity using endurance exercise in patients with established polymyositis and dermatomyositis: a multicenter randomized controlled trial with a 1-year open extension followup. Arthritis Care Res (Hoboken). 201312;65(12):1959–68. [PubMed: 23861241]
50. Gil-Ramírez A, Caz V, Smiderle FR, Martin-Hernandez R, Largo C, Tabernero M, et al.Water-Soluble Compounds from Lentinula edodes Influencing the HMG-CoA Reductase Activity and the Expression of Genes Involved in the Cholesterol Metabolism. J Agric Food Chem. 201639;64(9):1910–20. [PubMed: 26877235]
51. Zeng L, Yan J, Luo L, Zhang D. Effects of Pu-erh tea aqueous extract (PTAE) on blood lipid metabolism enzymes. Food Funct. 20156;6(6):2008–16. [PubMed: 26018873]
52. Endo AMonacolin K, a new hypocholesterolemic agent produced by a Monascus species. J Antibiot (Tokyo). 19798;32(8):852–4. [PubMed: 500505]
53. Limaye V, Bundell C, Hollingsworth P, Rojana-Udomsart A, Mastaglia F, Blumbergs P, et al.Clinical and genetic associations of autoantibodies to 3-hydroxy-3-methyl-glutaryl-coenzyme a reductase in patients with immune-mediated myositis and necrotizing myopathy. Muscle Nerve. 20158;52(2):196–203. [PubMed: 25521389]
54. Kadoya M, Hida A, Hashimoto Maeda M, Taira K, Ikenaga C, Uchio N, et al.Cancer association as a risk factor for anti-HMGCR antibody-positive myopathy. Neurol Neuroimmunol Neuroinflamm. 201612;3(6):e290.
55. Hengstman GJ, van Venrooij WJ, Vencovsky J, Moutsopoulos HM, van Engelen BG. The relative prevalence of dermatomyositis and polymyositis in Europe exhibits a latitudinal gradient. Ann Rheum Dis. 20002;59(2):141–2. [PubMed: 10666171]
56. Takeguchi-Kikuchi S, Hayasaka T, Katayama T, Kano K, Takahashi K, Saito T, et al.Anti-signal Recognition Particle Antibody-positive Necrotizing Myopathy with Secondary Cardiomyopathy: The First Myocardial Biopsy- and Multimodal Imaging-proven Case. Intern Med. 2019111;58(21):3189–94. [PubMed: 31292376]
57. Rider LG, Shah M, Mamyrova G, Huber AM, Rice MM, Targoff IN, et al.The myositis autoantibody phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine (Baltimore). 20137;92(4):223–43. [PubMed: 23877355]