Immune checkpoint inhibitor-related myositis: from pathophysiology to treatment

C. Sundarrajan¹, S. Bhai¹², M.M. Dimachkie³

¹Department of Neurology, UT Southwestern Medical Center, Dallas, TX;
²Neuromuscular Center, Institute for Exercise and Environmental Medicine, Texas Health Presbyterian, Dallas, TX;
³Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA.
Chandrasekhar Sundarrajan, BA
Salman Bhai, MD*
Mazen M. Dimachkie, MD*
*Co-last authors.
Please address correspondence to:
Salman Bhai
Department of Neurology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, 75390 Dallas TX, USA.
E-mail: salman.bhai@utsouthwestern.edu
Received on December 1, 2022; accepted in revised form on December 9, 2022.
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Key words: myositis, neoplasms, autoimmunity, immunotherapy, immune checkpoint inhibitors

ABSTRACT
With rapid advances in immuno-oncology, immune checkpoint inhibitors (ICIs) are increasingly used for a broad array of malignancies. This has led to a novel spectrum of adverse effects including ICI-related myositis, a potentially life-threatening neuromuscular complication that must be diagnosed and treated promptly. Significant gaps exist in the current understanding of ICI-related myositis due to the rarity of the condition and the lack of evidence-based guidelines, prompting the need to synthesise the most relevant and recent published works in the field. This review provides a broad overview of ICI-related myositis with an emphasis on pathophysiology, epidemiology, clinical features, workup, management and future directions.

Introduction
Immunotherapy has radically transformed cancer treatment, and immune checkpoint inhibitors (ICIs) lie at the forefront of this revolution. As immune checkpoint inhibitory receptors such as those associated with programmed cell death 1 (PD-1), PD ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are highly expressed on cancer cells, they allow cancer cells to evade immunosurveillance and to proliferate. ICIs promote continued non-specific T-cell activation and increased anti-tumour response leading to response in a good number of refractory or disseminated cancers (1). There has been considerable progress in the treatment of even advanced-stage cancers such as metastatic melanoma, with ICIs inducing complete remission in a subset of patients (2, 3). Following this success, the utilisation of ICIs has expanded to a growing number of malignancies (4). As of November 2022, nine ICIs targeting PD-1, PD-L1 and CTLA-4 have been approved by the United States Food and Drug Administration (FDA), and these are summarised in Table I (5-7).

Unfortunately, the increased activation of the immune system by ICIs can have the unintended consequence of targeting non-tumour cells, leading to the emergence of immune-related adverse effects (irAEs) (8). irAEs are distinct from side effects encountered in conventional cancer therapies and can target any organ system. The range of rheumatologic and neurologic manifestations is broad and can include polymyalgia rheumatica, Sjögren’s syndrome, scleroderma, sarcoidosis, encephalitis, hypophysitis, peripheral neuropathy, myasthenia gravis, and myositis (9-11). Myositis induced by ICI therapy is shown to carry a particularly high mortality rate when associated with other autoimmune manifestations such as myocarditis and myasthenia gravis (9, 12). Importantly, ICI-related myositis has features distinct from typical inflammatory myopathies and requires a different clinical approach to diagnosis and management (13).

With rising rates of ICI use, it is increasingly important for clinicians to be aware of ICI-induced myositis to ensure prompt diagnosis and treatment of this potentially life-threatening condition. This review aims to summarise the pathophysiology, epidemiology, clinical features, workup, and management of ICI-related myositis, while also highlighting knowledge gaps and future directions.

Immune pathophysiology
The anti-tumour response is a highly complex process, and the PD-1/PD-L1 and CTLA-4 checkpoints act at different stages of this pathway. CTLA-4...
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Table I. FDA-approved immune checkpoint inhibitors (PD-1/PD-L1/CTLA-4).

<table>
<thead>
<tr>
<th>Initial FDA approval</th>
<th>Drug</th>
<th>Target</th>
<th>FDA-approved indications</th>
</tr>
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<tbody>
<tr>
<td>2011</td>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Melanoma, CRC, HCC, mesothelioma, NSCLC, RCC</td>
</tr>
<tr>
<td>2014</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma, NSCLC, SCLC, RCC, Hodgkin's lymphoma, HNSCC, CRC, gastric cancer, HCC, urothelial carcinoma, oesophageal cancer, mesothelioma</td>
</tr>
<tr>
<td>2016</td>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Urothelial carcinoma, NSCLC, SCLC, breast cancer, HCC, melanoma</td>
</tr>
<tr>
<td>2017</td>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Merkel cell carcinoma, urothelial carcinoma, RCC</td>
</tr>
<tr>
<td>2017</td>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>Urothelial carcinoma, NSCLC, SCLC, biliary tract cancer, HCC</td>
</tr>
<tr>
<td>2018</td>
<td>Cemiplimub</td>
<td>PD-1</td>
<td>Cutaneous squamous cell carcinoma, BCC, NSCLC</td>
</tr>
<tr>
<td>2021</td>
<td>Dostarlimab</td>
<td>PD-1</td>
<td>Endometrial carcinoma, dMMR solid cancers</td>
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<tr>
<td>2022</td>
<td>Tremelimumab*</td>
<td>CTLA-4</td>
<td>HCC, NSCLC</td>
</tr>
</tbody>
</table>


*Approved in combination with durvalumab for HCC (Oct 2022) and NSCLC (Nov 2022).

inhibits naive T-cell activation primarily in the lymph nodes. Blocking CTLA-4 therefore results in continued activation of T-cells that can travel to peripheral tissues such as the tumour bed, where PD-1/PD-L1 interaction has similar inhibitory effects on T-cell activity. With prolonged exposure to tumour antigens, effector T cells in the tumour bed may lose the ability to respond to tumour antigens. This process is termed T-cell exhaustion and is facilitated by the interaction of PD-1 and PD-L1 checkpoints. Hence, blocking either PD-1 or its ligands allows for continued T-cell activation at the tumour site (14, 15).

In ICI-related myositis, T-cell activation is targeted toward healthy skeletal muscle, consisting of CD4+ and CD8+ T-cell and macrophage infiltration noted on skeletal muscle biopsy (16, 17). Marked necrosis may also be seen in a multifocal pattern, as opposed to a more homogenous pattern noted in the idiopathic inflammatory myopathies (IIMs) (18). Other patterns similar to those seen in dermatomyositis have been described, including perimysial perivascular inflammation and a tendency towards perifascicular atrophy (19). In patients with concomitant myocarditis, endomyocardial biopsy shows lymphocytic infiltration in a similar pattern to that seen in skeletal muscle and the prognosis of ICI myocarditis is poor (12, 16). It has been suggested that shared epitopes by tumour, skeletal muscle, and cardiac muscle could be responsible for this phenomenon (20-22). Unlike the IIMs, myositis-specific autoantibodies are generally not observed in ICI-related myositis (23, 24). Some patients present with acetylcholine receptor (AChR) antibodies which may suggest a concomitant myasthenia gravis (25). However, as AChR antibodies can also be seen in ICI-related myositis without myasthenia gravis, it has been suggested that AChR positivity may also be a nonspecific marker of autoimmune activation (26). Direct extraocular muscle inflammation is not uncommon in ICI myositis leading to diplopia which can be incorrectly assumed to be due to myasthenia gravis rather than myositis. Striational antibodies have been shown to be present in about half of patients with ICI-related myositis and even more pronounced in cases of concomitant myositis and myasthenia gravis (18, 23, 27). It is unclear if these antibodies may already be present before ICI initiation as Shah et al. noted in one patient (24). Statin-associated necrotising autoimmune myopathy (SANAM) is associated with autoantibodies directed at the 5-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) (11). A case report described muscle weakness and markedly elevated creatine kinase 2 weeks after ICI initiation in a patient with a history of statin intolerance (28). HMGCR antibody levels were initially normal then elevated at the time of weakness onset and further increased later on. ICI may have uncovered or exacerbated latent SANAM as this patient myalgias led to stopping rosuvastatin 2 weeks before ICI initiation. Though it is unclear if the myositis was mediated by the HMGCR antibodies, this case raises the question of whether pre-existing autoimmunity predisposes to ICI-related myositis. Kadota et al. propose that there are two different subsets of ICI-associated myositis with differing pathophysiology: a de novo onset type and an exacerbation after initiation of ICIs. In the latter subset, patients may already have predisposed autoreactive T-cells that are then activated after initiation of ICIs (29). Ti et al. found that patients with pre-existing antibodies (rheumatoid factor, antinuclear antibody, anti-thyroglobulin, and anti-thyroid peroxidase) had a higher predisposition to developing several types of irAEs but also carried a better prognosis than those without pre-existing antibodies (30). On the other hand,
a recent prospective study by Barth et al. did not reveal any association between autoantibody status and frequency of irAEs or treatment efficacy (31). Of note, these studies have examined a broad spectrum of irAEs, and more research is needed to examine these findings specifically with regards to ICI-related myositis.

**Epidemiology**
ICI-related myositis is a relatively rare entity, accounting for 0.38-0.6% of irAEs after ICI use (12, 13, 32). Nguyen et al. recently investigated ICI-related myositis cases in the World Health Organisation’s pharmacovigilance database and reported a male predominance (70%) with an average presenting age of 71. ICI-related myositis is more than twice as likely to occur with PD-1/PD-L1 inhibitors compared to CTLA-4 inhibitors, and combination therapy is significantly more likely to cause ICI-related myositis compared to monotherapy. Of the rheumatologic and musculoskeletal irAEs, myositis is the most severe, with a case fatality rate of 26.8% when associated with myasthenia gravis and 51.3% when concurrent with myocarditis (32). Lung and skin cancers are the most common malignancies associated with ICI-related myositis but also the most common indications for ICI therapy (9, 13, 32). It is likely that the epidemiology of ICI-related myositis will evolve as ICIs are used for a broader variety of indications.

**Clinical presentation**
ICI-induced myositis typically presents within two months after the initiation of ICIs but can be as early as 5 days or delayed up to 19 weeks with relatively quick progression over days to weeks (9, 17). As with idiopathic inflammatory myopathies, patients commonly present with progressive proximal upper and lower extremity weakness. Myalgias and fatigue are also common. However, oculomotor and bulbar symptoms can be seen in up to 25% of patients, which are rare in idiopathic inflammatory myopathies (33). These symptoms include ptosis, ophthalmoplegia, and dysphagia. There have also been reports of diaphragmatic involvement (34-36).

The presence of ocular, bulbar, and respiratory symptoms can resemble myasthenia gravis and therefore requires further workup with antibody testing, electromyography (EMG), repetitive nerve stimulation and possibly single fiber EMG to assess the integrity of the neuromuscular junction.

The frequency of ICI-related myositis and mortality risk are increased with combination ICI therapy. Large database analyses of myositis after combined nivolumab and ipilimumab therapy have reported frequencies of 0.24% and mortality of 0.03%, compared to 0.15% and 0.01%, respectively, with nivolumab only (20). Dyspnoea, chest pain, and arrhythmias should raise suspicion for myocarditis, which can occur concurrently in 11-41% of patients with ICI-related myositis and is a major cause of mortality (12, 13, 21, 32, 37). Interestingly, Hamada et al. reported that ptosis at symptom onset was independently and significantly associated with increased risk of developing concomitant myocarditis (13). Patients with overlapping myositis and myocarditis may also have an earlier onset of disease (20). Of note, overlapping asymptomatic myocarditis has also been reported and it is therefore important to assess for myocarditis in all patients with ICI-related myositis regardless of symptomatology (38). Lastly, the characteristic skin findings of dermatomyositis (for example, Gottron papules, heliotrope rash) are exceedingly rare in ICI-related myositis but have been described in the literature (39, 40).

With the clinical presentation of ICI-related myositis ranging from mild weakness to life-threatening myocarditis and respiratory failure, classification criteria are helpful for standardising the reporting of symptoms. The Common Terminology Criteria for Adverse Events (CTCAE), developed by the National Institutes of Health (NIH) and National Cancer Institute (NCI), grades immune related adverse events from cancer therapy (41). Grades 1 and 2 indicate mild or moderate weakness, grade 3 suggests severe weakness, grade 4 involves life-threatening consequences, and grade 5 indicates treatment-related death. The grading of ICI-related myositis has treatment implications and will be detailed in the Management section.

**Differential diagnoses and work-up**
Diagnosing ICI-related myositis can be challenging, especially since there are no established, evidence-based diagnostic criteria and no specific biomarkers. As discussed, the clinical presentation of ICI-related myositis is like that of IIMs but with additional features in some patients including ocular, bulbar, respiratory, and cardiac involvement. In any patient on ICI therapy, it is important to maintain a high index of suspicion for irAEs and particularly myositis given its relatively quick onset and potential for life-threatening myocardial involvement.

Given a pre-existing cancer diagnosis, it can be difficult to distinguish between true ICI-induced myositis and IIMs associated with malignancy. Differentiating these conditions is important for determining the next step in management. Importantly, the presence of myositis-specific antibodies and myositis-associated antibodies favours IIM instead of ICI-related myositis. Shibata et al. 2019 reports a case of a gentleman developing myositis after induction of nivolumab initially suspected to have ICI-related myositis. However, the high anti-TIF1-γ antibody titer and the presence of Gottron papules before initiation of ICI therapy led to the final diagnosis of malignancy-associated dermatomyositis (42). Hence, recent ICI therapy should not preclude the diagnosis of an IIM of paraneoplastic aetiology. Of note, progression of the underlying cancer should also be on the differential for patients presenting with generalised fatigue and weakness. Another potential confounder is Lambert-Eaton myasthenic syndrome (LEMS). It presents with proximal weakness, reduced tendon reflexes and dysautonomia. Fifty percent of LEMS cases have an underlying malignancy, most commonly small cell lung cancer (43).

The ocular, bulbar, and respiratory symptoms often noted in ICI-related myositis can also resemble features of ICI-related myasthenia gravis (MG),
which has an incidence of 0.24% (44). ICI-related myositis, however, typically does not present with the fluctuation in muscle fatigability seen in ICI-related myasthenia gravis. While MG antibodies such as anti-AChR, muscle specific kinase (MuSK), and low density lipoprotein receptor-related protein 4 (LRP4) can assist in the diagnosis, ICI-related myasthenia gravis can be seronegative in a third of patients and present as an overlapping syndrome with ICI-related myositis, complicating the distinction between these two entities (13, 36, 45).

Important laboratory tests to initially obtain include creatine kinase (CK), liver transaminases (AST/ALT), LDH, aldolase, and inflammatory markers (ESR, CRP) (21, 46). CK levels are generally elevated and correlate with symptom severity, with patients treated with combination ICIs having particularly high levels (23, 29, 47). Rise in CK occurs early in the clinical course, which can be helpful in initial workup (17). However, high CK levels are nonspecific and should be interpreted with caution. Liewluck et al. reported a patient in their ICI-related myositis cohort with very high CK levels but a mild course and acknowledged that it is possible that this patient had only rhabdomyolysis and not myositis (48).

There have also been reports of patients with ICI-related myositis only mildly elevated or normal CK. Shelly et al. noted that patients with oculobulbar predominant phenotype had lower CK levels (18).

Troponins should also be drawn, even in absence of cardiac symptoms, given the strong association of ICI-related myositis with myocarditis. Troponin I is more specific for cardiac involvement than troponin T, which can be elevated due to skeletal muscle breakdown as well (47). EKG is recommended to assess for arrhythmias, and echocardiogram and cardiac magnetic resonance imaging (MRI) can also be considered on an individual basis (49).

Imaging and EMG can help support the diagnosis of myositis, but findings are not specific for ICI-related myositis. EMG typically shows myopathic motor unit potentials and nerve conduction studies (NCS) can also help identify overlapping neuromuscular diseases (37, 47). While the pattern of myopathy with irritability supports the broad category of myositis on EMG, NCS and specifically repetitive nerve stimulation may suggest MG or LEMS. On limb MRI, affected muscles may show increased T2 signal indicative of oedema with contrast enhancement that at times involves the fascia suggesting added fascitis (19). Muscles also demonstrate increased FDG uptake on PET/CT. Muscle MRI and EMG can also guide the location of tissue biopsy as sampling the wrong area may provide a false negative result. The presence of endomysial inflammatory infiltrates on muscle biopsy and necrosis/myophagocytosis in a multifocal pattern is typical of ICI-related myositis (18). Perimysial perivascular inflammation and a tendency towards perifascicular atrophy have also been described with ICI-related myositis (19). Of note, performing biopsy after initiation of steroid therapy can affect results, though it is unclear how quickly results are affected (47).

With many reports in the form of isolated case studies, series and retrospective analyses, the inclusion criteria for ICI-related myositis varies between studies. To facilitate coordination among future studies, Saygin et al. recently proposed criteria for the diagnosis of ICI-related myositis. Major criterion was defined as muscle histopathology consistent with ICI-related myositis, and minor criteria were defined as 1) elevation in CK or aldolase, 2) EMG with myopathic pattern, and 3) abnormal signal on MRI or increased FDG uptake on PET scan. Among patients on ICI therapy with weakness or myalgia, one major or three minor criteria qualified as “definite” ICI-related myositis, whereas two minor criteria qualified as a “probable” diagnosis (37). These criteria have yet to be prospectively validated.

Management

The management of ICI-related myositis depends on the clinical presentation and extent of disease. In general, patients should be referred to a neurologist or rheumatologist in mild cases and hospitalised in severe cases. The mainstay of treatment is short-term corticosteroids and at times adjuvant immunosuppressive agents. Also of importance is the question of whether to stop or proceed with ICI treatment, which can affect overall cancer prognosis.

The American Society of Clinical Oncology (ASCO) and the Society for Immunotherapy for Cancer (SITC) have published similar guidelines for the treatment of ICI-related myositis stratified by CTCAE classification (46, 50). In grade 1 disease, characterised by mild weakness, patients can continue ICI therapy while being closely monitored for the development of any additional symptoms. Outpatient oral prednisone at 0.5 mg/kg/day could be considered if muscle weakness is accompanied by an increase in CK or aldolase. In grade 2 myositis, which involves moderate weakness and limitation of daily activities, ICI therapy should be withdrawn though it can be reinitiated if CK normalises, and symptoms are well controlled with a prednisone dosage of 10 mg or less. Treatment of grade 3 and 4 disease requires a higher prednisone dose of 1 mg/kg/day and potential escalation to pulse dosing of intravenous methylprednisolone. Most patients experience improvement with steroids (47). Corticosteroids should be slowly tapered over 4 weeks to limit cancer recurrence risk and it is important to remain vigilant for myositis relapse during this period (51). Symptoms may take days to months to resolve, and laboratory markers such as CK, ESR, and CRP should be followed.

Unfortunately, there are no clear guidelines for approaching steroid-refractory cases. Plasma exchange (PLEX), intravenous immunoglobulin (IVIG), and nonsteroidal immunosuppressive agents may be used in these scenarios. Patients with overlapping syndromes such as myasthenia gravis and myocarditis have been reported to be less responsive to steroid therapy (52). Therefore, it is important to be cognisant of these overlapping conditions when developing treatment plans. For example, management of ICI-related myocarditis requires higher doses of corticosteroids than ICI-related myositis, and therefore patients with overlapping ICI-related

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myositis and myocarditis may benefit from higher doses of corticosteroids upfront (52-54). Safa et al. reported that in cases of overlapping myasthenia gravis, early addition of PLEX or IVIG to the steroid regimen resulted in better outcomes regardless of initial symptom severity (44). Of note, plasma exchange can lower CK and it is important to be aware of this when monitoring for improvement (55).

Non-steroidal immunosuppressive agents such as rituximab, and possibly TNF-alpha inhibitors, and IL-6 antagonists can be attempted if there is still no improvement after steroids and IVIG or PLEX, but data are often anecdotal and mostly from case reports and series (50, 56). Caution with use of TNF-alpha blockers is recommended as they can trigger myositis whereas the randomised controlled trial of tocilizumab in the treatment of refractory adult myositis was negative (57, 58). Azathioprine, mycophenolate, and methotrexate can also be employed, as in HMs, but can take months to have a therapeutic effect (12, 59, 60).

Reinitiating ICI therapy after recovery from ICI-related myositis is done on a case-by-case basis, and formal guidelines have not yet been established. This requires a discussion between the treating oncologist and the muscle specialist and should include the patient. The risks of recurrent immune adverse events need to be balanced with the benefits of ICIs in cancer treatment.

Aldrich et al. reported that one patient in their study with overlapping myositis and myasthenia gravis developed a relapse after rechallenging, which suggests the need for greater caution in higher grade myositis (12). Weill et al. reported that none of the 9 patients in their national multicentre study that were rechallenged with ICIs had a relapse of myositis, though one patient developed immune-related colitis. Of note, none of the patients in the study had myocardial involvement, and some patients were excluded from rechallenge due to severity and safety reasons (61). Hence, ICI rechallenge appears to be a potentially feasible option after deliberation between the muscle and cancer specialist and the patient with careful consideration of the clinical presentation and severity of disease. If after weighing the risks benefits and alternatives the joint decision is made to move forward with ICI rechallenge, this should be done with caution and close patient monitoring of muscle status by the neurologist or rheumatologist.

Knowledge gaps and future directions

There are significant gaps in the current understanding of ICI-related myositis, beginning at the level of immune pathogenesis. The role of autoantibodies in ICI-related myositis is unclear, and more data on autoantibody status prior to ICI therapy initiation and genetic makeup may be helpful to identify factors that predispose certain patients to the development of myositis. Clearer mechanistic understanding of the ICI-induced toxicity in muscle can also guide treatment strategies. A particularly pressing unresolved issue is the best treatment of steroid-refractory ICI-related myositis or in cases with partial response requiring long-term treatment; prospective studies are needed to determine optimal management. More research is needed to determine if when and in whom ICI therapy can be reinitiated after successful treatment. Lastly, given the recent development of ICIs and improvements in cancer survival, the long-term safety profile of ICIs is unknown and continued monitoring of patients with a history of ICI-related myositis is essential. Ultimately, predicting which patients are at risk of developing myositis, prompt recognition and management of the complications, and selective re-initiation of the ICI are gaps that require further research.

Conclusion

Immune checkpoint inhibitors have revolutionised cancer therapy but have also introduced a new spectrum of side effects distinct from those seen with traditional cancer treatments. ICI-related myositis is a rare but serious adverse event that requires early recognition and prompt treatment. Clinical presentation is variable and can range from mild weakness to respiratory failure and myocarditis. Thorough workup is needed for diagnosis and exclusion of comorbid irAEs such as myocarditis and MG. Corticosteroids are the cornerstone of management and severe cases typically require adjunctive therapeutics in addition to stopping ICI therapy. Translational research to clarify the underlying pathophysiology and prospective clinical studies involving a larger number of patients will be crucial in efforts to better predict and most effectively treat ICI-related myositis while not interfering with the beneficial impact of ICIs on tumour control.

Competing interests

S. Bhai has received Advisory board honoraria and/or consulting fees from Pfizer, Alnylam, Alexion, Octapharma, Grifols, Argenx, Ig National Society, National Home Infusion Association, Taysha Gene Therapies. M.M. Dimachkie serves or recently served as a consultant for Abcuro, Amazentis, ArgenX, Astellas, Catalyst, Cello, Covance/Labcorp, CSL-Behring, EcoRI, Janssen, Kezar, MDA, Medlink, Momenta, NuFactor, Octapharma, Prio- vant, RaPharma/UCB, Roivant Sciences Inc, Sanofi Genzyme, Shire Takeda, Scholar Rock, Spark Therapeutics, Abata/Third Rock, UCB Biopharma and UpToDate. He received research grants or contracts or educational grants from Alexion, Alnylam Pharmaceuticals, Amicus, Biomarin, Bristol-Myers Squibb, Catalyst, Corbus, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Kezar, Mitsubishi Tanabe Pharma, MDA, NIH, Novartis, Octa- pharma, RaPharma/UCB, Sanofi Gen- zymes, Sarepta Therapeutics, Shire, Takeda, Spark Therapeutics, The Myosi- tis Association, UCB Biopharma/RaP- harma, Viromed/Healixmith and TMA. C. Sundarrajan has declared no com- peting interests.

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