Dermatomyositis: Diagnosis and treatment

Reid Waldman, MD,[a] Madeline E. DeWane, BA,[b] and Jun Lu, MD[a]
Farmington, Connecticut

Learning objectives
After completing this learning activity, participants should be able to describe initial workup for a suspected case of DM (including the role of auto-antibody testing) as well as recently updated diagnostic criteria; identify appropriate screening measures for both adults and children with DM; choose appropriate treatment for adults and children with DM and discuss the potential roles of emerging immunologic therapies in DM.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

The second article in this continuing medical education series reviews the initial evaluation of patients with suspected dermatomyositis (DM), the relevant work-up for malignancy and interstitial lung disease once a diagnosis of DM is made, and treatment recommendations for patients with DM based on disease severity, the presence of systemic symptoms, and myositis-specific antibody (MSA) profiles. This review emphasizes the emerging role of MSAs in the diagnosis of DM and highlights how MSAs can be used to guide the appropriate work-up for malignancy and interstitial lung disease. The treatment approach proposed by this continuing medical education series discusses both established and novel therapies for DM and highlights the importance of considering lesion type, degree of muscle involvement, presence of systemic symptoms, presence of MSAs, and patient age when determining the best treatment approach for a patient with DM. (J Am Acad Dermatol 2020;82:283-96.)

Key words: anti-MDA5 dermatomyositis; cancer-associated dermatomyositis; dermatomyositis; juvenile dermatomyositis.

The evaluation and management of patients with suspected dermatomyositis (DM) is evolving. The second article in this continuing medical education series reviews the initial evaluation of patients with suspected DM and the relevant work-up for systemic manifestations once a diagnosis is made. Recommendations for treatment based on disease severity, the presence of

From the University of Connecticut Department of Dermatology[a] and the University of Connecticut School of Medicine,[b] Farmington.
Funding sources: None.
Conflicts of interest: None disclosed.
Accepted for publication May 11, 2019.
Reprint requests: Jun Lu, MD, Department of Dermatology, University of Connecticut, 21 South Rd, Farmington, CT 06032. E-mail: jlu@uchc.edu.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2019.05.105
Date of release: February 2020
Expiration date: February 2023

Scanning this QR code will direct you to the CME quiz in the American Academy of Dermatology's (AAD) online learning center where after taking the quiz and successfully passing it, you may claim *1 AMA PRA Category 1 credit*. NOTE: You must have an AAD account and be signed in on your device in order to be directed to the CME quiz. If you do not have an AAD account, you will need to create one. To create an AAD account: go to the AAD's website: www.aad.org.

Abbreviations used:

EULAR/ACR:	European League Against Rheumatism/American College of Rheumatology
ILD:	interstitial lung disease
IVIG:	intravenous immunoglobulin
JDM:	juvenile dermatomyositis
JKI:	Janus kinase inhibitor
MMF:	mycophenolate mofetil
MSA:	myositis-specific antibody
MTX:	methotrexate
RP-ILD:	rapidly progressive interstitial lung disease

systemic symptoms, the presence of myositis-specific antibodies (MSAs), and patient age will be given. The integration of MSAs into the management of patients with DM will be emphasized. Treatment recommendations include a discussion of emerging therapies.

THE INITIAL APPROACH: DIAGNOSING DERMATOMYOSITIS

The initial evaluation of patients with suspected DM must include a total body skin examination, objective muscle strength examination, and a laboratory work-up.[1] In equivocal cases, obtaining a biopsy specimen of the skin or muscle or muscle imaging may clarify the diagnosis.[2] Historically, a diagnosis of DM was made based on criteria proposed by Bohan and Peter in 1975.[3] Many new classification systems have subsequently been proposed (Table I). Most recently, the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) developed the first validated classification criteria with a reported sensitivity of 87% and specificity of 82% for a diagnosis of DM. However, the sensitivity of these guidelines is poor for diagnosing amyopathic DM because only limited types of cutaneous lesions are included in their scoring system.[4,5] In addition, the only MSA included in the EULAR/ACR criteria is anti-Jo-1, because other antibodies were not widely available at the time the guidelines were formed.[1]

We have modified the EULAR/ACR diagnostic approach to incorporate the use of multiple newly available MSAs (Table II and Fig 1). The incorporation of MSAs into diagnostic criteria of DM is beneficial for several reasons: 1) it facilitates the diagnosis of DM, especially in cases of clinically amyopathic DM (CADM); 2) it separates patients with DM into clinically relevant subsets (which helps tailor the additional work-up for systemic manifestations based on an individual's MSA profile); and 3) it obfuscates the need for obtaining a biopsy specimen of the muscle in many cases. A 2018 study in *JAMA Neurology* supports the use of MSAs in diagnosis; in this study, patients with idiopathic inflammatory myopathies were appropriately classified as having DM, inclusion body myositis, immune-mediated necrotizing myositis, or antisynthetase syndrome based solely on MSA profile and clinical manifestations.[6]

EVALUATION FOR SYSTEMIC MANIFESTATIONS

Once a diagnosis of DM has been confirmed, patients must undergo additional work-up to identify systemic manifestations. This work-up should be directed by the patient's MSA profile. An in-depth review of the clinical manifestations associated with each MSA is provided in the first article in this continuing medical education series. Dermatologists using MSAs as part of their clinical decision making must ensure that they are ordering a testing assay that reliably detects and discriminates between relevant MSAs because some assays perform less reliably than others.[7,8]

Malignancy work-up

The estimated prevalence of malignancy in adult patients with DM is 20%. The risk of developing malignancy is highest within a year of diagnosis and remains elevated for ≤5 years.[9] Malignancy risk is also increased for males and those >45 years of age at the time of diagnosis.[9,10] In juvenile dermatomyositis (JDM), malignancy is extremely uncommon with no cases of malignancy-associated JDM identified in the EuroMyositis registry.[11] As highlighted in the first article in this continuing medical education series, malignancy-associated DM primarily occurs in adults who are either anti−transcription intermediary factor 1− or anti−nuclear matrix protein 2−positive.[11,12]

Patients with JDM do not require any work-up for malignancy.[11] A suggested algorithm for appropriate malignancy screening in newly diagnosed adult patients with DM is detailed in Fig 2. Adult patients with DM who are both anti−transcription intermediary factor 1− and anti−nuclear matrix protein 2−negative (ie, who have a low risk of malignancy-associated DM) require history, physical examination, "age-appropriate" cancer screening, and symptom-targeted cancer screening alone because there is not strong evidence to suggest that individuals without these antibodies are at an appreciably elevated risk for malignancy compared with the general population.[12] Aggressive work-up for

Table I. Classification systems for idiopathic inflammatory myopathies

Classification system	Criteria included	Entities defined	Benefits and limitations
Bohan and Peter (1975)[3,80]	Clinical: skin rash (heliotrope rash or Gottron sign) and symmetric proximal muscle weakness Laboratory: elevation of skeletal muscle enzymes Other: EMG and muscle biopsy specimen findings	Definite DM, probable DM, possible DM, definite PM, probable PM, and possible PM	High sensitivity but low specificity[81]; outdated conceptualization of DM and PM as related entities on a spectrum of inflammatory myopathy[82]; does not specify how to exclude other forms of myopathy[81]
Tanimoto et al (1995)[83]	Clinical: skin rash (heliotrope rash or Gottron sign or linear extensor erythema), proximal muscle weakness, muscle pain on grasping or spontaneous pain, nondestructive arthritis or arthralgia, and fever Laboratory: elevated CK or aldolase, elevated CRP or ESR, and positive anti-Jo-1 antibodies Other: abnormal EMG and muscle biopsy specimen findings	DM and PM	High sensitivity but low specificity[81]
Targoff et al (1997)[84]	Clinical: skin rash (heliotrope rash or Gottron sign) and symmetric proximal muscle weakness Laboratory: elevation of skeletal muscle enzymes and presence of any MSA Other: EMG and muscle biopsy specimen findings	Definite IIM, probable IIM, possible IIM, subclassifies DM, IBM, JDM, and ADM	Sensitivity 93% and specificity 89% using EULAR/ACR dataset[81]
Dalakas and Hohlfield (2003)[85]	Clinical: skin rash (or calcinosis) and myopathic muscle weakness Laboratory: elevated muscle enzymes Other: EMG and muscle biopsy specimen findings	Definite PM, probable PM, definite DM, probable DM, and definite ADM	High specificity but low sensitivity using EULAR/ACR dataset[81]
Hoogendijk et al (2003)[86]	Clinical: age, muscle weakness (specifies time course and pattern), and skin rash (heliotrope, periorbital edema, Gottron papules/ sign, V sign, shawl sign, holster sign) Laboratory: elevated CK and detection of MSAs Other: EMG, MRI, and muscle biopsy specimen findings	Definite DM, probable DM, ADM, DM sine dermatitis, definite PM, probable PM, nonspecific myositis, and IMNM	High specificity but low sensitivity using EULAR/ACR dataset[81]

Continued

Table I. Cont'd

Classification system	Criteria included	Entities defined	Benefits and limitations
EULAR/ACR (2017)[81]	Clinical: age, muscle weakness, and skin rash (heliotrope rash, Gottron papules, and Gottron sign) Laboratory: positive anti-Jo-1 antibody and elevated CK, LDH, AST, and ALT Other: muscle biopsy specimen findings	Algorithm determines IIM probability; subclassifies PM, IBM, DM, ADM, and JDM	Large dataset; sensitivity 93%, specificity 88% (with muscle biopsy data); sensitivity 87%, specificity 82% (without muscle biopsy data); subclassification limited by small sample size for some entities; requires additional validation in Asian and African populations; can diagnose DM without muscle biopsy when typical skin findings are present
Mariampillai et al (2018)[6]	47 variables used in multiple correspondence analysis, included sociodemographic variables, skin lesions, biological variables (including CK levels and MSAs), histologic variables, clinical muscular variables, and extramuscular variables	DM, IBM, IMNM, and ASS	

ADM, Amyopathic dermatomyositis; *ALT*, alanine aminotransferase; *ASS*, antisynthetase syndrome; *AST*, aspartate aminotransferase; *CK*, creatine kinase; *CRP*, C-reactive protein; *DM*, dermatomyositis; *EMG*, electromyographic; *ESR*, erythrocyte sedimentation rate; *EULAR/ACR*, European League Against Rheumatism/American College of Rheumatology; *IBM*, inclusion body myositis; *IIM*, idiopathic inflammatory myopathy; *IMNM*, immune-mediated necrotizing myositis; *JDM*, juvenile dermatomyositis; *LDH*, lactate dehydrogenase; *MSA*, myositis-specific antibody; *PM*, polymyositis.

Table II. Initial workup for suspected dermatomyositis based on European League Against Rheumatism/American College of Rheumatology criteria

Examination	History and physical examination	Total body skin examination, manual strength testing of bilateral extremities and neck flexors
Baseline laboratory testing	Muscle enzymes	Creatine kinase, lactate dehydrogenase, aspartate aminotransferase, and aldolase
Autoantibody testing	DM-specific autoantibodies	Mi2, TIF1, MDA5, NXP2, and SAE
	Antisynthetase syndrome autoantibodies	Jo-1, PL-7, PL-12, EJ, and OJ
	IMNM autoantibodies (if indicated clinically)	SRP and HMGCR
	Other connective tissue disease—related autoantibodies (if indicated clinically)	Antinuclear antibody, Ro/La, dsDNA, anti-Sm, and Scl-70
Additional testing	If the above testing is equivocal	T2-weighted MRI of area of weakness
	If diagnosis remains uncertain	Obtain biopsy specimen of muscle from affected area identified on MRI

DM, Dermatomyositis; *dsDNA*, double-stranded DNA; *HMGCR*, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; *IMNM*, immune-mediated necrotizing myositis; *MDA5*, anti—melanoma differentiation-associated protein 5; *MRI*, magnetic resonance imaging; *NXP2*, nuclear matrix protein 2; *SAE*, small ubiquitin-like modifier activating enzyme; *Scl-70*, topoisomerase 1; *SRP*, signal recognition particle; *TIF1*, transcription intermediary factor 1.

malignancy in these patients is likely to be costly and invasive, and the available evidence suggests that it is unlikely to improve outcomes. Possible exceptions to this recommendation are: 1) anti—small ubiquitin-like modifier activating enzyme—positive individuals, because some studies have demonstrated a risk for malignancy in these patients, although this finding has not been uniformly reproducible; and 2) MSA-negative patients, because a recent large, retrospective study suggested that these patients have a threefold elevated risk of developing malignancy over matched control subjects.[12]

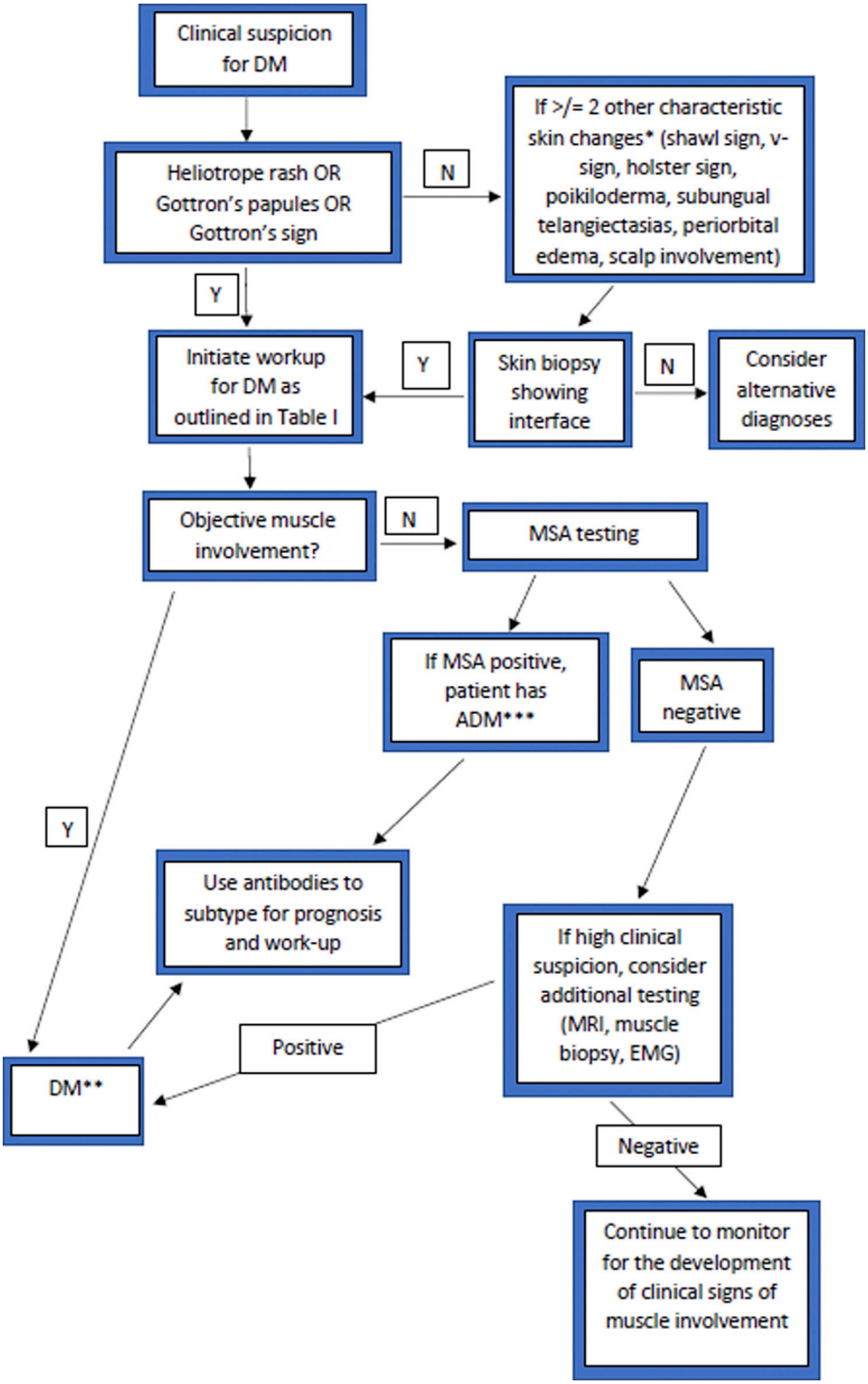

Fig 1. Diagnostic algorithm for adult and juvenile dermatomyositis (DM). *As indicated in the first article in this continuing medical education series Table I. **Pts <18 years of age at the time of symptom onset are considered to have juvenile dermatomyositis (JDM). ***Patients with amyopathic DM should be monitored regularly for the development of muscle involvement. *EMG*, Electromyography; *MRI*, magnetic resonance imaging; *MSA*, myositis-specific antibody.

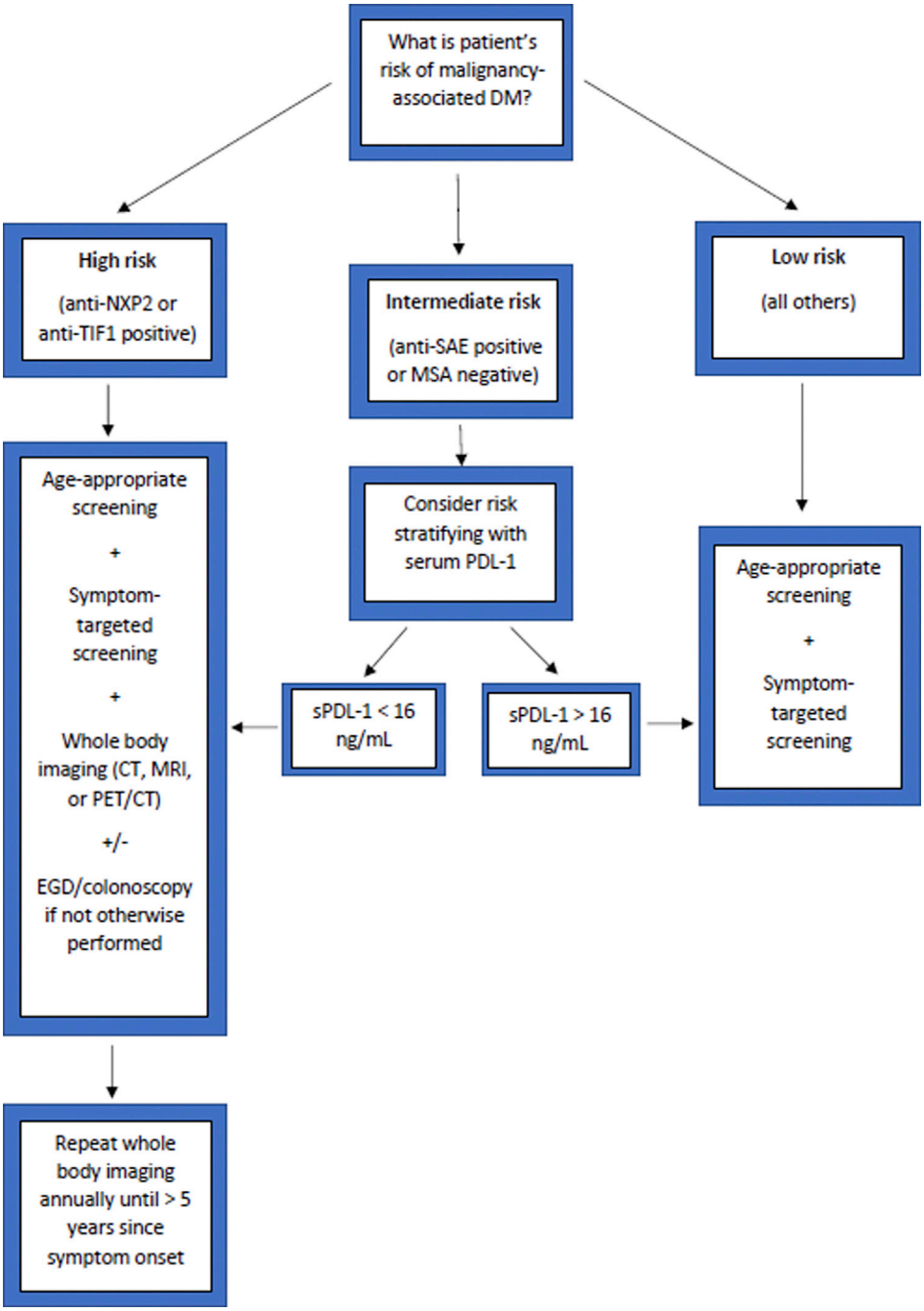

Fig 2. Malignancy work-up for newly diagnosed patients with dermatomyositis (DM). *CT*, Computed tomography; *MRI*, magnetic resonance imaging; *NXP2*, nuclear matrix protein 2; *PET-CT*, positron emission tomography-computed tomography; *SAE*, small ubiquitin-like modifier activating enzyme; *sPDL*, soluble programmed death ligand-1; *TIF1*, anti—transcription intermediary factor 1.

Given the paucity of data about cancer risk in these 2 subpopulations, it may be reasonable to further stratify cancer risk with serum biomarkers, although such an approach has never been studied or suggested for this "intermediate-risk" population specifically. Annual soluble programmed death ligand-1 measurements can be considered, because extremely elevated levels of soluble programmed death ligand-1 have been associated with malignancy in patients with DM.[13,14] The use of cancer

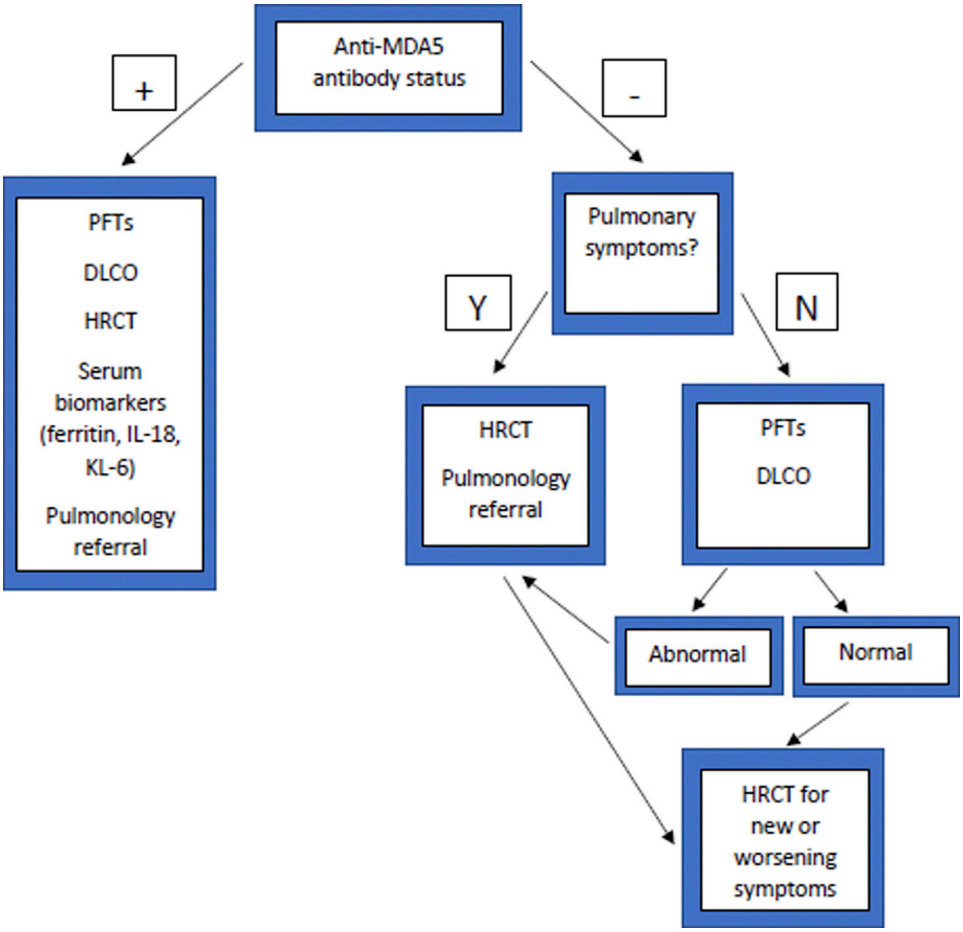

Fig 3. Interstitial lung disease work-up for newly diagnosed patients with dermatomyositis (DM). *DLCO*, Diffusion capacity of the lung for carbon monoxide; *HRCT*, high-resolution computed tomography; *IL-18*, interleukin-18; *KL-6*, Krebs von den Lungen-6; *MDA5*, anti—melanoma differentiation-associated protein 5; *PFT*, pulmonary function testing.

serum biomarkers (eg, CEA, CA 19-9) other than prostate-specific antigen, a potential component of age-appropriate screening, has not been demonstrated to be effective for detecting malignancy in patients with DM.[15]

In addition to age-appropriate and symptom-targeted malignancy screening, individuals who are anti—transcription intermediary factor 1— or anti—nuclear matrix protein 2—positive (ie, high-risk for malignancy-associated DM) should undergo whole body imaging with either computed tomography (CT), magnetic resonance imaging, or positron emission tomography CT.[13,16] These modalities have been proven to detect DM-associated malignancies that would be missed by age-appropriate and symptom-targeted screening.[17] No study has compared superiority of one imaging modality over the others. Studies that have failed to demonstrate benefit with the use of whole-body imaging have not subselected for high-risk patients.[18]

The appropriate reimaging interval in high-risk individuals who had an initially negative work-up for malignancy has not been studied. As an increased malignancy risk is present for ≤5 years after DM onset, some authorities recommend annual imaging until that time point is reached.[13] Finally, high-risk individuals who would not receive upper and lower endoscopy as part of their age-appropriate screening and who do not have malignancy identified on other work-ups should consider undergoing this testing.[13]

Interstitial lung disease work-up

Evaluation for interstitial lung disease (ILD) in patients with a new diagnosis of DM involves identifying whether a patient has ILD and, if so, whether a patient has a poor prognosis subset of ILD termed rapidly progressive ILD (RP-ILD). The early identification of RP-ILD is essential because it is fatal in ≤6 months in 50% of cases and the prognosis can be improved if treatment is initiated before the

development of abnormalities on high-resolution CT.[19,20]

Fig 3 provides an algorithm for evaluating patients with DM for ILD. All patients require pulmonary function testing and diffusion capacity of the lung for carbon monoxide at the time of diagnosis.[21] In asymptomatic patients with restrictive physiology present on pulmonary function testing and decreased diffusion capacity of the lung for carbon monoxide, or in patients with symptoms suggestive of ILD, high-resolution CT is indicated.[21] If ILD is not present on an initial work-up, patients can be monitored clinically with a plan to repeat high-resolution CT if new or worsening pulmonary symptoms develop.[21] All patients with evidence of ILD require an urgent pulmonology evaluation.

Anti–melanoma differentiation-associated protein 5 (MDA5) antibodies are present in at least half of all cases of DM-associated ILD and >80% of cases of DM-associated RP-ILD.[20,22,23] In JDM, anti-MDA5 positivity is also predictive of ILD and RP-ILD with an estimated sensitivity of ~70% for ILD.[24] Because RP-ILD can evade imaging during its early stages, testing serum biomarkers that correlate with the presence of ILD and that are elevated before imaging changes should be considered.[25,26] Elevated levels of serum ferritin, interleukin-18, Krebs von den Lungen-6, and anti-MDA5 antibodies themselves have been associated with the presence of ILD, and laboratory testing for these biomarkers should be considered in all patients with anti-MDA5 dermatomyositis.[27-31]

Other systemic work-up

The first article in this continuing medical education series discussed the many other potential systemic manifestations of DM and JDM. Given their relative infrequency, screening for these manifestations with a targeted review of symptoms is reasonable.

GENERAL TREATMENT APPROACH

Management of DM is nuanced; dermatologists frequently diagnose the disease and have primary responsibility for the cutaneous manifestations of the disease, but myopathy and other systemic manifestations often drive therapy. The appropriate treatment approach is determined by consideration of 5 factors:

1) Lesion type—Is the lesion nonvasculopathic (eg, shawl sign, heliotrope rash), vasculopathic (digital pulp ulcers, inverse Gottron papules), or calcinotic?
2) Degree of muscle involvement—Is the patient amyopathic/hypomyopathic? Does the patient have persistent cutaneous symptoms despite having controlled myopathy? Is the patient postmyopathic (ie, have the patient's muscle symptoms resolved despite being off treatment but residual cutaneous disease is still present)?
3) Presence of systemic symptoms—Are other organ systems involved? Is there an associated malignancy?
4) Presence of MSAs—What clinical subset does the patient have as suggested by the presence of MSAs?
5) Patient age—Does the patient have adult or juvenile dermatomyositis?

We discuss each of these factors with an emphasis on the use of a multidisciplinary approach in settings where muscle involvement or systemic symptoms are present.

Considering lesion type

Nonvasculopathic cutaneous disease. Three layers of therapy should be used for all patients with nonvasculopathic disease: sun protection, topical therapy with corticosteroids or calcineurin inhibitors, and systemic therapy.[32,33] This section will focus on systemic therapies. A treatment algorithm for adult DM is shown in Fig 4.

Systemic corticosteroids. Systemic corticosteroids are the gold standard initial treatment for DM-related myopathy. However, they should not be used in patients with CADM and should not be used as a monotherapy because this approach is frequently ineffective and associated with the development of unacceptable long-term adverse effects.[34-36] Similarly, in cases where a patient's myopathy is controlled with corticosteroids but cutaneous symptoms persist, a dose increase in corticosteroids alone is not recommended. A combination of systemic corticosteroids with oral immunosuppressants or biologics should be used at disease onset in patients with myopathy or other systemic symptoms, similar to how combination therapy is used in patients with bullous disorders to limit systemic corticosteroid use.[34,37]

Antimalarials. Traditional treatment algorithms have emphasized hydroxychloroquine as the first-line systemic agent for cutaneous DM. However, recent evidence suggests that patients treated with hydroxychloroquine are more likely to flare their cutaneous disease than they are to achieve satisfactory disease control from hydroxychloroquine monotherapy.[35,36,38,39] Patient MSA profiles may predict risk of cutaneous flare after hydroxychloroquine initiation with anti–small ubiquitin-like modifier activating enzyme–positive patients at the highest risk and anti-MDA5 patients without

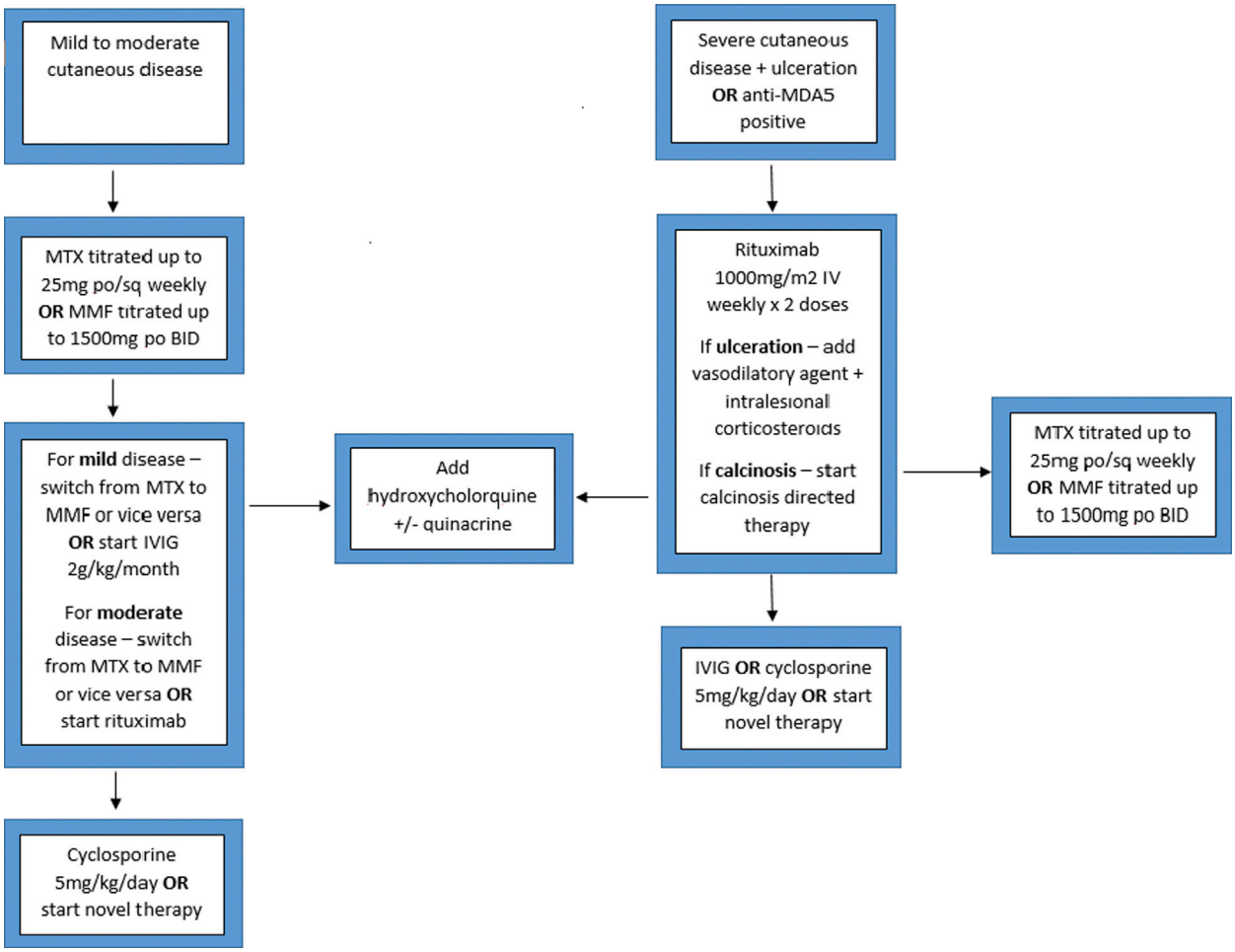

Fig 4. Adult dermatomyositis treatment algorithm. *BID*, Twice daily; *IV*, intravenous; *IVIG*, intravenous immunoglobulin; *MDA-5*, anti–melanoma differentiation-associated protein 5; *MMF*, mycophenolate mofetil; *MTX*, methotrexate.

demonstrable risk.[40] Furthermore, unlike other systemic therapies, none of the antimalarials have an effect on the noncutaneous manifestations of DM (eg, myopathy and ILD).[41,42] Given the favorable side effect profile of antimalarials, they can be considered as adjuvants when disease control is inadequate with other systemic agents.[35,36,42,43]

Mycophenolate mofetil and methotrexate. In the absence of vasculopathic or calcinotic lesions, the first-line systemic therapies for nonvasculopathic DM are mycophenolate mofetil (MMF) and methotrexate (MTX).[38,44-48] Both of these medications often require high dosing, with many adults requiring 3 g of MMF daily or 25 mg of MTX weekly. These medications should be started in conjunction with systemic corticosteroids when myopathy is present. However, systemic corticosteroids do not need to be used in conjunction with these medications when treating CADM or postmyopathic cutaneous disease.

There are no head-to-head studies comparing MMF and MTX, but several considerations may favor the use of one agent over the other; MTX often has faster onset (~4 weeks) and has clinical trial data supporting its use as a steroid-sparing agent. In addition, MMF is effective for treating ILD.[37,49,50] Treatment failure with one agent is not predictive of treatment failure with the other.

Rituximab. In cases where a combination of systemic corticosteroids and an oral immunosuppressant fail, rituximab is the appropriate next step in therapy.[51-53] In individuals with vasculopathic or calcinotic lesions, adults with anti-MDA5 positivity, or children with NXP-2 positivity, rituximab plus systemic corticosteroids can be considered first-line treatment.[54-56] Support for the use of rituximab comes from the largest clinical trial ever conducted for idiopathic inflammatory myopathies, the Rituximab in Myositis trial.[51] This trial demonstrated that 83% of children and adults with DM who

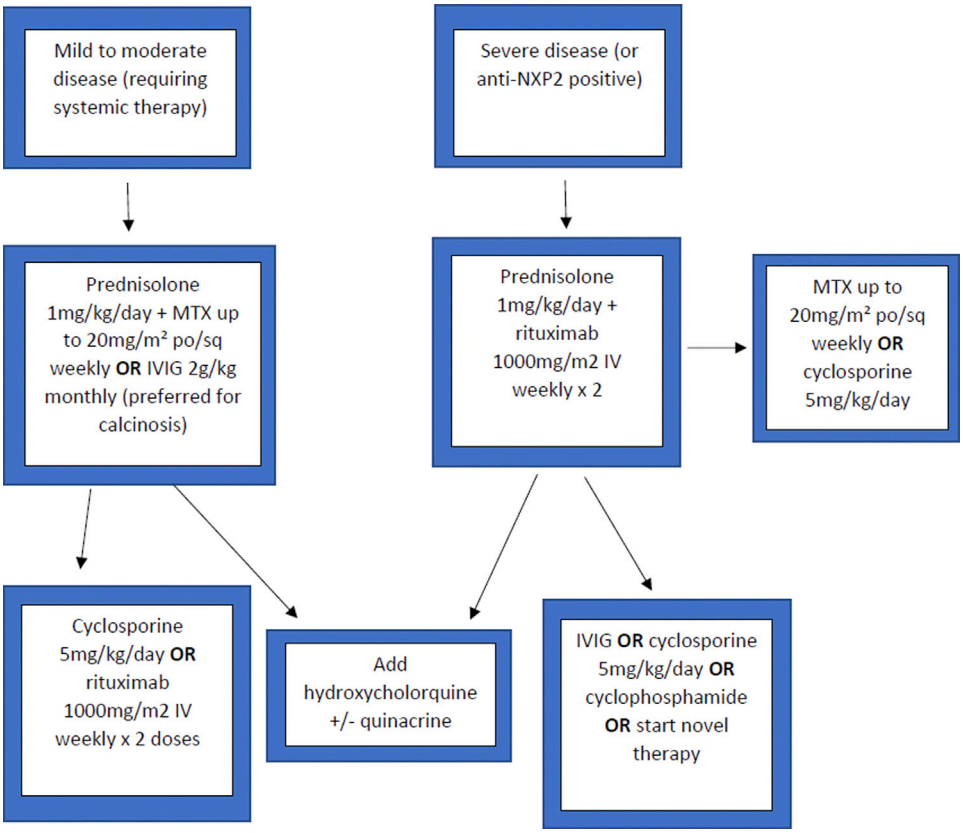

Fig 5. Juvenile dermatomyositis treatment algorithm. *IV*, Intravenous; *IVIG*, intravenous immunoglobulin; *MTX*, methotrexate; *NXP2*, nuclear matrix protein 2.

Table III. Emerging treatments for dermatomyositis

Drug	Route of administration	Mechanism of action	Ongoing clinical trial (Y/N)
Tocilizumab	IV	IL-6 inhibitor	Y
Aletuzumab	IV	Anti-CD52	N
Abatacept	IV	Costimulatory modulator	Y
Infliximab	IV	TNF inhibitor	Y
Anakinra	SubQ	IL-1 inhibitor	N
Eculizumab	IV	C5-blocking agent	N
Apremilast	PO	PDE4 inhibitor	Y

IL, Interleukin; *IV*, intravenous; *PDE4*, phosphodiesterase 4; *PO*, per os; *SubQ*, subcutaneous; *TNF*, tumor necrosis factor.

previously failed systemic corticosteroids and ≥1 immunosuppressant improved with rituximab and were tapered off systemic steroids more quickly.[51] MSA-positive individuals had a greater chance of responding favorably to rituximab than MSA-negative individuals.[51]

In addition, several recent findings suggest that rituximab may have disease-modifying properties. Rituximab is the only treatment associated with improvement in nailfold capillary abnormalities that may represent prevention of pathogenic vessel damage. In cases where MSAs are presumed to be pathogenic (eg, anti-MDA5 DM), rituximab likely works through a similar mechanism as in pemphigus (a condition in which it has been shown to be disease-modifying).[51,57] The 2 major limitations to the use of rituximab are that it has a slow onset and a risk of serious infection >6%.[51,56]

The frequency with which individuals receiving rituximab should undergo an additional round of treatment is unknown. In the Rituximab in Myositis trial, $CD19^+$ numbers rebounded above 5 cells/uL at weeks 32 to 36 on average.[51] Based on the pemphigus literature, it may be reasonable to trend peripheral B cell concentrations to guide therapy.[58]

Intravenous immunoglobulin. A reasonable treatment option in patients who have failed or who are intolerant of rituximab is intravenous immunoglobulin (IVIG).[43,59,60] It is also recommended for patients with controlled myopathy but persistent cutaneous disease.[61] In cases with severe disease that is refractory to IVIG, subcutaneous immunoglobulin administration can be considered if available.[62]

Calcineurin inhibitors. Calcineurin inhibitors (typically cyclosporine and less frequently tacrolimus) are reasonable third-line options or are useful in cases in which myopathy is controlled but other immunosuppressants are not controlling cutaneous disease.[48] Although cyclosporine is as effective as MTX based on Pediatric Rheumatology International Trials Organization data, MTX and MMF are preferred because the Pediatric Rheumatology International Trials Organization trial demonstrated that cyclosporine use was associated with a greater risk of serious adverse effects.[37] Calcineurin inhibitors are also a reasonable choice in patients with comorbid interstitial lung disease.[63,64]

Other traditional therapies. Other therapies that can be considered include infliximab, azathioprine, and cyclophosphamide. However, these should be reserved for refractory cases given the plethora of superior options listed above.[65-67]

Vasculopathic cutaneous disease. Vasculopathic skin lesions include ulceration, inverse Gottron papules, and nailfold capillary abnormalities. These lesions are notoriously refractory to immunosuppressive therapy and confer significant morbidity even in the absence of other cutaneous disease. The only systemic agent with robust data supporting its use for vasculopathic lesions is rituximab. However, rituximab alone is often ineffective for treating ulceration.[56,68] Intralesional corticosteroids are frequently used for treating ulcerations and inverse Gottron papules and may be effective, but recent evidence supports using vasodilatory agents. Case studies suggest that nifedipine, sildenafil, intravenous prostaglandins, and bosentan should be added as early adjuncts given the otherwise refractory nature of these lesions.[69]

Calcinosis cutis. Like vasculopathic lesions, calcinotic lesions are typically refractory to immunosuppressive therapy. Patients with JDM and calcinosis should be preferentially treated with IVIG because it has the best data supporting its use for calcinosis specifically.[59,70,71] For a detailed discussion of calcinosis cutis–directed therapies, we encourage readers to review the continuing medical education series on calcinosis cutis.[72]

Considering degree of muscle involvement

Patients with myopathy should be managed in conjunction with a rheumatologist or neurologist. Controlled cutaneous disease is not predictive of controlled myopathy and vice versa. Unlike in patients with CADM (for whom monotherapy with oral immunosuppressants is a reasonable first-line therapy), first-line therapy for management of the myopathy component of DM is the simultaneous initiation of corticosteroids and a steroid-sparing immunosuppressant (eg, MMF or MTX).[37] Subsequent treatment choices in individuals with recalcitrant myopathy are similar to those highlighted above for the treatment of refractory cutaneous disease.

The appropriate treatment for persistent cutaneous involvement in patients with controlled myopathy depends on the treatment the patient is currently receiving and the degree of severity of the cutaneous involvement.[73] Dose escalations of an oral immunosuppressant, initiation of hydroxychloroquine, initiation of IVIG, or initiation of rituximab can all be reasonable next steps depending on the clinical scenario.[61] Postmyopathic cutaneous disease can be managed similarly to CADM.

Considering systemic symptoms

Treatment of the systemic symptoms associated with DM is beyond the scope of this continuing medical education series and should be addressed as part of a multidisciplinary approach.

Considering MSAs. MSAs will undoubtedly be used to personalize treatment decisions for patients with DM in the future. However, currently there is a paucity of data supporting such an approach. Several anecdotally supported treatment considerations have been mentioned above.

Considering age. Only 2 clinical trials have specifically evaluated patients with JDM (the Pediatric Rheumatology International Trials Organization and Rituximab in Myositis trials), but consensus opinions are also available from the Childhood Arthritis and Rheumatology Research Alliance and Single Hub and Access Point for Pediatric Rheumatology in Europe registries.[37,51,56,74,75] Review of these pivotal studies supports the approach to JDM proposed in Fig 5. All patients should at least be started on a combination of systemic corticosteroids with either MTX or IVIG to decrease the long-term steroid burden.[37,75] In patients who fail first-line treatment, have severe disease with ulceration, calcinosis, or lipodystrophy at the time of presentation, or have poor-prognosis NXP-2 disease, rituximab plus systemic corticosteroids can be considered.[56] Other biologics, cyclophosphamide, and Janus kinase inhibitors can be considered in patients with refractory disease.[65,67,76]

Emerging treatments

Several novel approaches to DM have recently garnered significant interest. Janus kinase inhibitors (JKIs) will be discussed below because they have the most robust evidence for the treatment of cutaneous DM. Other emerging treatments are listed in Table III.

JKIs. DM is driven by type I interferons. Both in vivo and in vitro data have shown that JKIs

decrease levels of type I interferons in individuals with DM.[77] Case series have shown that several JKIs are effective for treating refractory cutaneous disease.[78] One series has also shown that JKIs may be an effective add-on therapy in patients with RP-ILD.[79] There is an ongoing clinical trial assessing the efficacy of tofacitinib in refractory DM that is assessing both skin and muscle outcomes.

In conclusion, a thorough initial assessment of patients with suspected DM is essential to making a diagnosis with as little delay and morbidity as possible. The management of DM is nuanced and requires a constant assessment for the development of systemic symptoms. A multi-disciplinary approach is recommended.

REFERENCES

1. Bottai M, Tjärnlund A, Santoni G, et al. EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups: a methodology report. *RMD Open*. 2017;3:e000507.
2. Ran J, Ji S, Morelli JN, Wu G, Li X. T2 mapping in dermatomyositis/polymyositis and correlation with clinical parameters. *Clin Radiol*. 2018;73:1057.e13-1057.e18.
3. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med*. 1975;292:344-347.
4. Hočevar A, Rotar Z, Krosel M, Čučnik S, Tomšič M. Performance of the 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies in clinical practice. *Ann Rheum Dis*. 2018;77:e90.
5. Patel B, Khan N, Werth VP. Applicability of EULAR/ACR classification criteria for dermatomyositis to amyopathic disease. *J Am Acad Dermatol*. 2018;79:77-83.e1.
6. Mariampillai K, Granger B, Amelin D, et al. Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies. *JAMA Neurol*. 2018;75:1528-1537.
7. Ghirardello A, Rampudda M, Ekholm L, et al. Diagnostic performance and validation of autoantibody testing in myositis by a commercial line blot assay. *Rheumatology (Oxford)*. 2010;49:2370-2374.
8. Victor J, Zanardo L, Héron-Mermin D, et al. Retrospective analysis of anti-TIF1gamma, anti-NXP2 and anti-SAE1/2 antibodies carriers at Bordeaux university hospital from November 2014 to February 2017 [in French]. *Rev Med Interne*. 2019;40:70-81.
9. Qiang JK, Kim WB, Baibergenova A, Alhusayen R. Risk of malignancy in dermatomyositis and polymyositis. *J Cutan Med Surg*. 2017;21:131-136.
10. Yang Z, Lin F, Qin B, Liang Y, Zhong R. Polymyositis/dermatomyositis and malignancy risk: a metaanalysis study. *J Rheumatol*. 2015;42:282-291.
11. Lilleker JB, Vencovsky J, Wang G, et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. *Ann Rheum Dis*. 2018;77:30-39.
12. Yang H, Peng Q, Yin L, et al. Identification of multiple cancer-associated myositis-specific autoantibodies in idiopathic inflammatory myopathies: a large longitudinal cohort study. *Arthritis Res Ther*. 2017;19:259.
13. Selva-O'Callaghan A, Martinez-Gómez X, Trallero-Araguás E, Pinal-Fernández I. The diagnostic work-up of cancer-associated myositis. *Curr Opin Rheumatol*. 2018;30:630-636.
14. Chen H, Peng Q, Yang H, et al. Increased levels of soluble programmed death ligand 1 associate with malignancy in patients with dermatomyositis. *J Rheumatol*. 2018;45:835-840.
15. Lim CH, Tseng CW, Lin CT, et al. The clinical application of tumor markers in the screening of malignancies and interstitial lung disease of dermatomyositis/polymyositis patients: a retrospective study. *SAGE Open Med*. 2018;6, 2050312118781895.
16. Li Y, Zhou Y, Wang Q. Multiple values of 18F-FDG PET/CT in idiopathic inflammatory myopathy. *Clin Rheumatol*. 2017;36:2297-2305.
17. Leatham H, Schadt C, Chisolm S, et al. Evidence supports blind screening for internal malignancy in dermatomyositis: data from 2 large US dermatology cohorts. *Medicine (Baltimore)*. 2018;97:e9639.
18. Maliha PG, Hudson M, Abikhzer G, Singerman J, Probst S. 18F-FDG PET/CT versus conventional investigations for cancer screening in autoimmune inflammatory myopathy in the era of novel myopathy classifications. *Nucl Med Commun*. 2019;40:377-382.
19. Kurasawa K, Arai S, Namiki Y, et al. Tofacitinib for refractory interstitial lung diseases in anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis. *Rheumatology (Oxford)*. 2018;57:2114-2119.
20. Chen Z, Cao M, Plana MN, et al. Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. *Arthritis Care Res*. 2013;65:1316-1324.
21. Vij R, Strek ME. Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. *Chest*. 2013;143:814-824.
22. Li L, Wang H, Wang Q, et al. Myositis-specific autoantibodies in dermatomyositis/polymyositis with interstitial lung disease. *J Neurol Sci*. 2019;397:123-128.
23. Ikeda S, Arita M, Morita M, et al. Interstitial lung disease in clinically amyopathic dermatomyositis with and without anti-MDA-5 antibody: to lump or split? *BMC Pulm Med*. 2015;15:159.
24. Tansley SL, Betteridge ZE, Gunawardena H, et al. Anti-MDA5 autoantibodies in juvenile dermatomyositis identify a distinct clinical phenotype: a prospective cohort study. *Arthritis Res Ther*. 2014;16:R138.
25. Nishioka A, Tsunoda S, Abe T, et al. Serum neopterin as well as ferritin, soluble interleukin-2 receptor, KL-6 and anti-MDA5 antibody titer provide markers of the response to therapy in patients with interstitial lung disease complicating anti-MDA5 antibody-positive dermatomyositis. *Mod Rheumatol*. 2018:1-7.
26. Kurtzman DJB, Vleugels RA. Anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis: a concise review with an emphasis on distinctive clinical features. *J Am Acad Dermatol*. 2018;78:776-785.
27. Hanaoka M, Katsumata Y, Kawasumi H, Kawaguchi Y, Yamanaka H. KL-6 is a long-term disease-activity biomarker for interstitial lung disease associated with polymyositis/dermatomyositis, but is not a short-term disease-activity biomarker. *Mod Rheumatol*. 2019;29:625-632.
28. Li L, Wang Q, Wen X, et al. Assessment of anti-MDA5 antibody as a diagnostic biomarker in patients with dermatomyositis-associated interstitial lung disease or rapidly progressive interstitial lung disease. *Oncotarget*. 2017;8:76129-76140.
29. Yang Y, Yin G, Hao J, Xie Q, Liu Y. serum interleukin-18 level is associated with disease activity and interstitial lung disease in

patients with dermatomyositis. *Arch Rheumatol*. 2017;32:181-188.
30. Kobayashi N, Takezaki S, Kobayashi I, et al. Clinical and laboratory features of fatal rapidly progressive interstitial lung disease associated with juvenile dermatomyositis. *Rheumatol (Oxford)*. 2015;54:784-791.
31. Sato S, Uejima Y, Nanbu M, et al. Clinical analysis and outcome of interstitial lung disease complicated with juvenile dermatomyositis and juvenile polymyositis. *Mod Rheumatol*. 2017;27:652-656.
32. Muro Y, Sugiura K, Akiyama M. Cutaneous manifestations in dermatomyositis: key clinical and serological features-a comprehensive review. *Clin Rev Allergy Immunol*. 2016;51:293-302.
33. Yoshimasu T, Ohtani T, Sakamoto T, Oshima A, Furukawa F. Topical FK506 (tacrolimus) therapy for facial erythematous lesions of cutaneous lupus erythematosus and dermatomyositis. *Eur J Dermatol*. 2002;12:50-52.
34. Kohsaka H, Mimori T, Kanda T, et al. Treatment consensus for management of polymyositis and dermatomyositis among rheumatologists, neurologists and dermatologists. *Mod Rheumatol*. 2019;29:1-19.
35. Anyanwu CO, Chansky PB, Feng R, Carr K, Okawa J, Werth VP. The systemic management of cutaneous dermatomyositis: results of a stepwise strategy. *Int J Womens Dermatol*. 2017;3:189-194.
36. Pinard J, Femia AN, Roman M, et al. Systemic treatment for clinically amyopathic dermatomyositis at 4 tertiary care centers. *JAMA Dermatol*. 2019;155:494-496.
37. Ruperto N, Pistorio A, Oliveira S, et al. Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial. *Lancet*. 2016;387:671-678.
38. Galimberti F, Li Y, Fernandez AP. Clinically amyopathic dermatomyositis: clinical features, response to medications and malignancy-associated risk factors in a specific tertiary-care-centre cohort. *Br J Dermatol*. 2016;174:158-164.
39. Pelle MT, Callen JP. Adverse cutaneous reactions to hydroxychloroquine are more common in patients with dermatomyositis than in patients with cutaneous lupus erythematosus. *Arch Dermatol*. 2002;138:1231-1233.
40. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med*. 1993;329:1993-2000.
41. Piguet V, Choy E. Dermatomyositis: a slow path towards targeted therapies or will conventional therapies prevail? *Br J Dermatol*. 2018;179:1233-1234.
42. Woo TY, Callen JP, Voorhees JJ, Bickers DR, Hanno R, Hawkins C. Cutaneous lesions of dermatomyositis are improved by hydroxychloroquine. *J Am Acad Dermatol*. 1984;10:592-600.
43. Callander J, Robson Y, Ingram J, Piguet V. Treatment of clinically amyopathic dermatomyositis in adults: a systematic review. *Br J Dermatol*. 2018;179:1248-1255.
44. Olivo Pallo PA, de Souza FHC, Miossi R, Shinjo SK. Mycophenolate mofetil in patients with refractory systemic autoimmune myopathies: case series. *Adv Rheumatol*. 2018;58:34.
45. Edge JC, Outland JD, Dempsey JR, Callen JP. Mycophenolate mofetil as an effective corticosteroid-sparing therapy for recalcitrant dermatomyositis. *Arch Dermatol*. 2006;142:65-69.
46. Gelber AC, Nousari HC, Wigley FM. Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. *J Rheumatol*. 2000;27:1542-1545.
47. Mainetti C, Terziroli Beretta-Piccoli B, Selmi C. Cutaneous manifestations of dermatomyositis: a comprehensive review. *Clin Rev Allergy Immunol*. 2017;53:337-356.
48. Isak V, Jorizzo JL. Recent developments on treatment strategies and the prognosis of dermatomyositis: a review. *J Dermatol Treat*. 2018;29:450-459.
49. Waldman R, Strober BE. Laboratory monitoring requirements during mycophenolate mofetil therapy for dermatologic conditions: a single institution retrospective chart review. *J Am Acad Dermatol*. 2019. https://doi.org/10.1016/j.jaad.2019.02.040 [Epub ahead of print].
50. Hayashi M, Kikuchi T, Takada T. Mycophenolate mofetil for the patients with interstitial lung diseases in amyopathic dermatomyositis with anti-MDA-5 antibodies. *Clin Rheumatol*. 2017;36:239-240.
51. Oddis CV, Reed AM, Aggarwal R, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. *Arthritis Rheum*. 2013;65:314-324.
52. Dinh HV, McCormack C, Hall S, Prince HM. Rituximab for the treatment of the skin manifestations of dermatomyositis: a report of 3 cases. *J Am Acad Dermatol*. 2007;56:148-153.
53. de Souza FHC, Miossi R, de Moraes JCB, Bonfá E, Shinjo SK. Favorable rituximab response in patients with refractory idiopathic inflammatory myopathies. *Adv Rheumatol*. 2018;58:31.
54. So H, Wong VTL, Lao VWN, Pang HT, Yip RML. Rituximab for refractory rapidly progressive interstitial lung disease related to anti-MDA5 antibody-positive amyopathic dermatomyositis. *Clin Rheumatol*. 2018;37:1983-1989.
55. Vargas Lebrón C, Ruiz Montesino MD, Moreira Navarrete V, Toyos Sainz de Miera FJ. Treatment with rituximab in juvenile dermatomyositis: effect on calcinosis. *Reumatol Clin*. 2019. https://doi.org/10.1016/j.reuma.2018.06.010. [in Spanish; Epub ahead of print].
56. Aggarwal R, Loganathan P, Koontz D, Qi Z, Reed AM, Oddis CV. Cutaneous improvement in refractory adult and juvenile dermatomyositis after treatment with rituximab. *Rheumatol (Oxford)*. 2017;56:247-254.
57. Argobi Y, Smith GP. Tracking changes in nailfold capillaries during dermatomyositis treatment. *J Am Acad Dermatol*. 2019;81:275-276.
58. Albers LN, Liu Y, Bo N, Swerlick RA, Feldman RJ. Developing biomarkers for predicting clinical relapse in pemphigus patients treated with rituximab. *J Am Acad Dermatol*. 2017;77:1074-1082.
59. Galimberti F, Kooistra L, Li Y, Chatterjee S, Fernandez AP. Intravenous immunoglobulin is an effective treatment for refractory cutaneous dermatomyositis. *Clin Exp Dermatol*. 2018;43:906-912.
60. Anh-Tu Hoa S, Hudson M. Critical review of the role of intravenous immunoglobulins in idiopathic inflammatory myopathies. *Semin Arthritis Rheum*. 2017;46:488-508.
61. Danieli MG, Calcabrini L, Calabrese V, Marchetti A, Logullo F, Gabrielli A. Intravenous immunoglobulin as add on treatment with mycophenolate mofetil in severe myositis. *Autoimmun Rev*. 2009;9:124-127.
62. de Inocencio J, Enríquez-Merayo E, Casado R, González-Granado LI. Subcutaneous immunoglobulin in refractory juvenile dermatomyositis. *Pediatrics*. 2016;137. https://doi.org/10.1542/peds.2015-3537.
63. Kotani T, Makino S, Takeuchi T, et al. Early intervention with corticosteroids and cyclosporin A and 2-hour postdose blood concentration monitoring improves the prognosis of acute/subacute interstitial pneumonia in dermatomyositis. *J Rheumatol*. 2008;35:254-259.
64. Shimojima Y, Ishii W, Matsuda M, Kishida D, Ikeda SI. Effective use of calcineurin inhibitor in combination therapy for

interstitial lung disease in patients with dermatomyositis and polymyositis. *J Clin Rheumatol*. 2017;23:87-93.
65. Schiffenbauer A, Garg M, Castro C, et al. A randomized, double-blind, placebo-controlled trial of infliximab in refractory polymyositis and dermatomyositis. *Semin Arthritis Rheum*. 2018;47:858-864.
66. Bunch TW, Worthington JW, Combs JJ, Ilstrup DM, Engel AG. Azathioprine with prednisone for polymyositis. A controlled, clinical trial. *Ann Intern Med*. 1980;92:365-369.
67. Deakin CT, Campanilho-Marques R, Simou S, et al. Efficacy and safety of cyclophosphamide treatment in severe juvenile dermatomyositis shown by marginal structural modeling. *Arthritis Rheumatol*. 2018;70:785-793.
68. Clottu A, Laffitte E, Prins C, Chizzolini C. Response of mucocutaneous lesions to rituximab in a case of melanoma differentiation antigen 5-related dermatomyositis. *Dermatology*. 2012;225:376-380.
69. Combalia A, Giavedoni P, Tamez L, Grau-Junyent JM, Mascaró JM. Bosentan for cutaneous ulcers in anti-MDA5 dermatomyositis. *JAMA Dermatol*. 2018;154:371-373.
70. Schanz S, Ulmer A, Fierlbeck G. Response of dystrophic calcification to intravenous immunoglobulin. *Arch Dermatol*. 2008;144:585-587.
71. Shahani L. Refractory calcinosis in a patient with dermatomyositis: response to intravenous immune globulin. *BMJ Case Rep*. 2012;2012. https://doi.org/10.1136/bcr-2012-006629.
72. Reiter N, El-Shabrawi L, Leinweber B, Berghold A, Aberer E. Calcinosis cutis: part II. Treatment options. *J Am Acad Dermatol*. 2011;65:15-22.
73. Huber AM, Kim S, Reed AM, et al. Childhood Arthritis and Rheumatology Research Alliance consensus clinical treatment plans for juvenile dermatomyositis with persistent skin rash. *J Rheumatol*. 2017;44:110-116.
74. Spencer CH, Rouster-Stevens K, Gewanter H, et al. Biologic therapies for refractory juvenile dermatomyositis: five years of experience of the Childhood Arthritis and Rheumatology Research Alliance in North America. *Pediatr Rheumatol Online J*. 2017;15:50.
75. Enders FB, Bader-Meunier B, Baildam E, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. *Ann Rheum Dis*. 2017;76:329-340.
76. Papadopoulou C, Hong Y, Omoyinmi E, Brogan PA, Eleftheriou D. Janus kinase 1/2 inhibition with baricitinib in the treatment of juvenile dermatomyositis. *Brain*. 2019;142:e8.
77. Ladislau L, Suárez-Calvet X, Toquet S, et al. JAK inhibitor improves type I interferon induced damage: proof of concept in dermatomyositis. *Brain J Neurol*. 2018;141:1609-1621.
78. Kurtzman DJB, Wright NA, Lin J, et al. Tofacitinib citrate for refractory cutaneous dermatomyositis: an alternative treatment. *JAMA Dermatol*. 2016;152:944-945.
79. Kato M, Ikeda K, Kageyama T, et al. Successful treatment for refractory interstitial lung disease and pneumomediastinum with multidisciplinary therapy including tofacitinib in a patient with anti-MDA5 antibody-positive dermatomyositis. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis*. 2019. https://doi.org/10.1097/RHU.0000000000000984 [Epub ahead of print].
80. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med*. 1975;292:403-407.
81. Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis*. 2017;76:1955-1964.
82. Suzuki S, Uruha A, Suzuki N, Nishino I. Integrated Diagnosis Project for Inflammatory Myopathies: an association between autoantibodies and muscle pathology. *Autoimmun Rev*. 2017;16:693-700.
83. Tanimoto K, Nakano K, Kano S, et al. Classification criteria for polymyositis and dermatomyositis. *J Rheumatol*. 1995;22:668-674.
84. Targoff IN, Miller FW, Medsger TA, Oddis CV. Classification criteria for the idiopathic inflammatory myopathies. *Curr Opin Rheumatol*. 1997;9:527-535.
85. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet*. 2003;362:971-982.
86. Hoogendijk JE, Amato AA, Lecky BR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10—12 October 2003, Naarden, The Netherlands. *Neuromuscul Disord*. 2004;14:337-345.