# Anti-MDA5-positive dermatomyositis and remission in a single referral centre population

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## Abstract

### Objective

*To describe a single-centre North American adult cohort of anti-MDA5-positive dermatomyositis patients, with emphasis on drug-free long-term remission.*

### Methods

*We conducted an observational retrospective cohort study of anti-MDA5-positive DM patients. All consented patients seen in the Johns Hopkins Myositis Centre from 2003-2020 with suspected muscle disease were routinely screened for myositis-specific autoantibodies. All sera were screened for anti-MDA5 autoantibodies by line blot; positives were verified by enzyme-linked immunoassay. Patients whose sera were anti-MDA5 positive by both assays (n=52) were followed longitudinally. If clinical status was unavailable, structured telephone interviews were conducted. Clinical remission was defined as being off all immunosuppression >1 year while remaining asymptomatic.*

### Results

*38/52 (73%) of the patients were women with a median age at disease-onset of 47 (IQR 40-54). Twenty-five of the patients (48%) were White, 16 (30%) were Black and 3 (6%) were Asian. Most patients (42/52, 80%) had interstitial lung disease, defined by inflammatory or fibrotic changes on high resolution computed tomography (HRCT). 18/52 (35%) of patients required pulse-dose methylprednisolone, 4/52 (8%) experienced spontaneous pneumothorax/pneumomediastinum, 6/52 (12%) required intubation, and 5/52 (10%) died. Over longitudinal follow-up (median 3.5 years), 9 (18%) patients achieved clinical remission. The median time from symptom onset to clinical remission was 4 years, and the median duration of sustained remission was 3.5 years (range 1.4-7.8). No demographic or disease characteristics were significantly associated with remission.*

### Conclusion

*In this single centre, tertiary referral population of anti-MDA5-positive dermatomyositis, ~20% of patients experienced long-term drug-free remission after a median disease duration of 4 years. No clinical or biologic factors were associated with clinical remission.*

**Key words**

dermatomyositis, interstitial lung disease, MDA protein, remission

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*Competing interests: page 314.*

## Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune syndromes characterised by proximal muscle weakness and skeletal muscle inflammation. The discovery of myositis specific autoantibodies (MSAs) has been instrumental in defining more homogenous patient subgroups within IIM, informing diagnosis, clinical monitoring and treatment decisions. Anti-melanoma differentiation-associated gene 5 (MDA5) autoantibodies define a specific subgroup of dermatomyositis (DM) patients characterised by hypo- or amyopathic muscle disease, distinct cutaneous features and risk of rapidly progressive interstitial lung disease (RP-ILD)(1,2). Since the original description of MDA5 antibodies in 2005(3), published data has focused on clinical predictors and biomarkers of severe disease, often defined as RP-ILD and/or mortality. However, few studies in adult anti-MDA5-positive DM populations have examined the subgroup of patients who experience clinical remission. In this report, we describe a large single centre North American cohort of adult anti-MDA5-positive DM, with an emphasis on the subgroup of patients who experience drug-free, long-term clinical remission.

## Methods

*Patient population*

Serum from 2,595 consecutively evaluated patients seen in the Johns Hopkins Myositis Centre from 2003-2020 with suspected inflammatory and non-inflammatory muscle diseases was routinely banked, and screened for MSAs by Euroimmun line blot myositis panel (Lubeck, Germany). While the majority of patients were enrolled at the Johns Hopkins outpatient clinic, our IRB-approved protocol allows for enrolment of patients in the hospital setting as well. All patients consented into the Johns Hopkins Myositis Research Registry under IRB no. IRB00235256, and provided written informed consent to publish the results. Of the 2,595 consented patients, 1,412 patients had a diagnosis of inflammatory myopathy by either Bohan and Peter criteria or the EULAR/ACR Classification Criteria (excluding inclusion body myositis) (4-6), of whom 67 were positive for anti-MDA5 antibodies. These 67 sera were subsequently tested for MDA5 antibodies by enzyme-linked immunoassay (ELISA, manufactured by MBL, Nagoya, Japan); anti-MDA5 antibodies were confirmed in 52/67 sera. Only sera that were positive by both assays (n=52) were included in this study. The 15 patients who were positive by line blot but negative by ELISA all had DM by Bohan and Peter criteria with a median line blot anti-MDA5 titre of 18 (IQR 17-26, range 16-38). All 15 patients had other MSAs by line blot including 4 anti-Jo1, 4 anti-TIF1γ, 2 anti-Mi2b, 2 anti-SAE, 1 anti-Mi2a, 1 anti-NXP2, and 1 anti-PM100. Data on demographics and disease characteristics was obtained from the Johns Hopkins Myositis Research Registry, including manual muscle testing, muscle enzymes, pulmonary function testing, high-resolution computed tomography (HRCT) reports, and cutaneous signs of Heliotrope/Gottron's/calcinosis/cutaneous ulcerations were recorded as discrete variables. Spirometry and lung volume results (forced vital capacity [FVC], total lung capacity [TLC], and diffusing capacity of carbon monoxide DLCO]) were reported as the nadir percent predicted measured over longitudinal follow-up by a test of good or fair quality. Intubation was recorded if attributed to progressive ILD and respiratory failure (*e.g.* elective intubations or intubation for non-DM causes were excluded). Pneumothorax/pneumomediastinum were considered present only if spontaneous (those post-procedure or occurring while on mechanical ventilation were excluded). A board-certified chest radiologist (CTL) reviewed the CT images most proximal to DM symptom onset, and categorised them based on the American Thoracic Society-European Respiratory Society Classification (7). Ulcerations were further divided into ischemic digital ulcers, skin ulcerations, and mucosal/oropharyngeal ulcerations (excluding patients on methotrexate or with suspected herpesvirus). Myositis symptom-onset was defined as the first symptom documented in the electronic

**Table I.** Demographic and disease characteristics of entire anti-MDA5 Cohort, as well as those who experienced clinical remission. Ro52 antibody status was determined by Euroimmun. Physical examination findings are reported as ever/never recorded throughout longitudinal follow-up.

| Total n=51 | | Chronic course (n=42) Median (IQR) | Remission (n=9) Median (IQR) | *p*-value |
|---|---|---|---|---|
| Patient age at IIM symptom onset | 47.3 (39.7-54.3) | 47.6 (39.7-53.8) | 47.1 (42.1-59.9) | 0.770 |
| Patient age at cohort entry | 48.8 (41.1-55.3) | 49.2 (41.1-55.0) | 48.0 (43.3-61.3) | 0.880 |
| Male sex | 27% | 26% | 33% | 0.690 |
| Race | | | | 0.700 |
| White | 47% | 45% | 56% | |
| Black | 31% | 33% | 22% | |
| Asian | 6% | 7% | 0% | |
| Other | 10% | 7% | 22% | |
| Declined | 2% | 2% | 0% | |
| Unknown | 4% | 5% | 0% | |
| Ethnicity | | | | 0.610 |
| Hispanic | 2% | 2% | 0% | |
| Not Hispanic | 86% | 83% | 100% | |
| Unknown | 12% | 14% | 0% | |
| Duration of follow-up | 3.7 (1.4-5.9) | 3.8 (1.7-6.3) | 1.8 (1.1-3.8) | 0.130 |
| Ro52 Positive | 42% | 38% | 56% | 0.460 |
| Gottron's sign or papules | 98% | 98% | 100% | 1.000 |
| Heliotrope sign | 75% | 76% | 67% | 0.680 |
| Synovitis on physical examination | 57% | 57% | 56% | 1.000 |
| Calcinosis on physical examination | 35% | 36% | 33% | 1.000 |
| Elevated CPK | 15% | 19% | 0% | 0.320 |
| Maximum CPK | 101.0 (52.0-160.0) | 106.5 (52.0-177.0) | 56.0 (48.0-92.0) | 0.130 |
| Maximum aldolase | 8.7 (6.9-10.8) | 8.4 (6.9-10.8) | 9.1 (6,4-12.6) | 0.550 |
| History of malignancy (ever) | 12% | 12% | 13% | 1.000 |
| ILD on high-resolution CT | 60% | 81% | 78% | 1.000 |
| Nadir FVC over longitudinal follow-up | 70.5 (57.5-85.5) | 75.0 (59.0-86.0) | 59.0 (51.0-69.0) | 0.096 |
| Nadir TLC over longitudinal follow-up | 68.5 (59.0-79.0) | 70.0 (59.0-80.0) | 61.0 (58.0-72.5) | 0.320 |
| Nadir DLCO over longitudinal follow-up | 62.5 (45.5-78.5) | 62.0 (45.5-79.5) | 68.0 (51.0-78.0) | 0.600 |
| Ulcerations (composite) (digital ulcers, cutaneous ulcers, and mucosal ulcers) | 67% | 71% | 44% | 0.140 |
| Ischaemic digital ulcers on examination or pits | 31% | 31% | 33% | 1.000 |
| Mucosal ulcerations (tongue, larynx, vocal cords, mouth, NOT attributable to MTX or HS | 35% | 34% | 43% | 0.690 |
| Cutaneous ulcerations on skin (hands or rest of body) | 63% | 67% | 44% | 0.270 |
| Required intubation for rapidly progressive ILD | 12% | 14% | 0% | 0.570 |
| Spontaneous pneumothorax or pneumomediastinum | 8% | 10% | 0% | 1.000 |
| Proximal muscle weakness on examination | 73% | 79% | 44% | 0.093 |
| Received pulse dose methylprednisolone | 35% | 40% | 11% | 0.130 |
| Death | 10% | 12% | 0% | 0.570 |

MTX: methotrexate; HS: herpes simplex virus.

medical record by the patient limited to the following: arthralgia, dyspnoea, myalgia, weakness, or rash consistent with DM. All patients were contacted in 2019-2020 to update clinical status if not longitudinally followed in clinic. Given a majority of our MDA5 patients were enrolled and followed in the early 2000s, we do not have systematic collection of IMACS disease activity measures or Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) scores. In patients no longer followed in our centre, a detailed systematic telephone interview was conducted to assess all organ systems including skin, joint, lung, and muscle. Remission was defined as a patient being off all immunosuppressive and immunomodulatory therapies >1 year while remaining asymptomatic (lack of arthralgias, dyspnoea, myalgias, weakness or rash). For an outcome comparison cohort, 51 randomly selected anti-Jo-1 positive patient sera (defined as >15/+ Units on Euroimmun line blot) from the Johns Hopkins Myositis Centre Registry were studied. The choice of anti-Jo-1 patients as a comparator group was informed by the similarity of disease phenotypes between anti-MDA5 and anti-Jo1 patients (*e.g.* high prevalence of ILD and inflammatory arthritis). These 51 anti-Jo1 patients were matched to the anti-MDA5 cohort for disease duration within 1 year.

*Statistical analysis*

Descriptive statistics were reported for demographic and clinical characteristics. Student's t-test, Fisher exact, and Wilcoxon rank sum were used to compare subgroups and performed using Stata v. 14 (College Station, Texas).

## Results

*Patient characteristics*

Demographic and disease characteristics for the anti-MDA5-positive DM cohort can be found in Table I. Fifty of the 52 (96%) met the definition of probable or definite DM as defined by the 2017 EULAR/ACR classification criteria(6). The additional two patients had DM characterised by Gottron's sign, ILD,

Mechanic's hands, and calcinosis. Of the 52 patients, 39 (75%) were referred from an outside rheumatologist, 4 (8%) were referred directly from primary care, 3 (6%) from dermatology, 2 (4%) from pulmonary, and 4 (8%) presented directly to a hospital and subsequently referred to our myositis centre.

Thirty-eight (73%) of the patients were women. The median age at DM symptom-onset was 47 (IQR 40-54). Twenty-five (48%) patients were White, 16 (30%) were Black, 3 (6%) were Asian and 8 (16%) were other/declined to provide race. All patients had either Heliotrope or Gottron's sign, 29 (56%) had synovitis, and 18 (35%) had calcinosis. A total of 73% of patients displayed proximal muscle weakness throughout follow-up, though most patients had normal muscle enzymes. The maximum median CPK was 101 units/L (IQR 50–160) and aldolase was 8.8 units/L (IQR 6.9–10.8). The majority of patients (42/52, 80%) had ILD, defined by inflammatory or fibrotic changes on HRCT. With regards to disease severity, 4/52 (8%) experienced a spontaneous pneumothorax or pneumomediastinum, 6/52 (12%) required intubation, and 5/52 (10%) died. 18/52 (35%) of patients required pulse-dose methylprednisolone at some point in their treatment course. Over longitudinal follow-up, the median of which was 3.5 years (IQR 1.3–5.9), 9/51 (18%) patients achieved clinical remission. One patient lost to follow-up could not be reached to ascertain clinical status. Compared to all other races combined, Black patients were found to have a significantly younger age of DM-symptom onset (median 42 [IQR 38-48] *vs*. 50 [IQR 44–55], $p$=0.034) and higher maximum CPK (median 154 (IQR 85–467) *vs*. 76 (IQR 48-120), $p$=0.002). No other clinical features or outcomes were significantly different between races.

*Characteristics associated with disease remission and death*

For the 9 patients who achieved clinical remission, the median time from DM-symptom onset to clinical remission was 4 years (IQR 2.4-5.0, range 1.8–5.6). Of note, disease duration was calculated in two separate ways: DM-symptom onset to last clinical office visit, and DM-symptom onset to research phone interview. The median duration of sustained remission at the time of this study was 3.5 years (range 1.4–7.8). None of the patients relapsed during the period of observation. No demographic or disease characteristics were significantly associated with clinical remission, although these patients tended to have less cutaneous ulcerations (44% *vs*. 71%, $p$=0.05) and were less likely to present with muscle weakness (44% *vs*. 67%, $p$<0.05). Moreover, the majority of the patients that achieved remission were more likely to have NSIP compared to the patients with chronic disease (88% *vs*. 22%, $p$<0.0001). None of the patients in remission had developed RP-ILD.

For the five patients who died, the median time from DM-symptom onset to death was 1.8 years (IQR 0.7–2.3, range 0.4–6.9). The cause of death for all patients was respiratory failure (RP-ILD in three, and ILD in the presence of infectious complications in two). The five patients who died over follow-up were more likely to require intubation for RP-ILD, develop spontaneous pneumothoraxes or mediastinum, and receive pulse dose methylprednisolone ($p$<0.05 for all comparisons). Age, sex, race, and other disease characteristics were not significantly associated with mortality.

In the anti-Jo1-positive IIM comparison cohort, we ascertained the frequency of remission and death. Of the 51 patients, 7/51 (14%) died (all-cause mortality) and 7/51 (14%) achieved remission (Supplementary Table S1). As expected, patients with anti-Jo1 positive IIM were more likely to have muscle involvement (94% *vs*. 73%, $p$=0.004), higher maximum CPK levels (median 720.0 [IQR 221.5–2162.0] *vs*. 101.0 [IQR 52.0–160.0], [$p$<0.0001), and less likely to have cutaneous manifestations, that are more common in patients with anti-MDA5 positive DM (Supplementary Table S1).

**Table II.** Radiographic pattern of initial HRCT scan for the 34 patients who had available imaging files.

| Initial HRCT Pattern n=34 | Chronic n=28 | Remission n=6 |
|---|---|---|
| Definite UIP (honeycombing) | 7% | 0% |
| Probable UIP (without honeycombing) | 4% | 0% |
| Fibrotic NSIP | 11% | 50% |
| Cellular/inflammatory NSIP | 11% | 33% |
| OP | 29% | 0% |
| Mixed | 7% | 0% |
| DAD/AIP | 4% | 0% |
| Unclassified | 7% | 0% |
| Normal | 21% | 17% |

UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonia; DAD: diffuse alveolar damage; AIP: acute interstitial pneumonia; OP: organising pneumonia.

*Pulmonary findings*

Of the 52 patients, CT chest reports were available for 51 (98%) and CT images were available for 34/52 (65%). The disease duration from DM-symptom onset to first chest HRCT (n=51) was 8 months (median 7 months, IQR 2.6–18). Of the 34 available studies, 11 had a non-specific interstitial pneumonia (NSIP) pattern (six with fibrotic subtype, five with cellular/inflammatory), eight had organising pneumonia (OP) pattern, three had usual interstitial pneumonia (UIP) pattern, two had mixed patterns (OP/NSIP and OP/UIP), one had diffuse alveolar damage/acute interstitial pneumonitis (DAD/AIP) pattern, and one was unclassified (Table II). Notably, 8/34 patients had no ILD detected on their initial CT scan. Of the eight patients, four had follow-up imaging, three of which demonstrated fibrotic changes. The median time between initial scan and follow-up imaging in these four patients was 248 days. Of the 9 patients who went into remission, 6 had HRCT images for review: 5/6 had NSIP pat-

tern (three fibrotic, two cellular/inflammatory *vs*. three and three respectively for the patients with chronic disease, $p$=0.05), none had OP (*vs*. 8 patients with chronic disease) and one had no evidence of ILD.

*Treatment history*

A wide spectrum of immunosuppressive and immunomodulatory agents was utilised to treat patients with anti-MDA5-positive DM, reflecting the clinical heterogeneity of organ involvement (Table III). The three most common immunosuppressant medications patients received (including before entry into our cohort) were corticosteroids (94%), mycophenolate (71%), and azathioprine (51%). Among the 52 patients, combination therapy was typical, with the majority of patients (79%) receiving at least 3 medications concurrently at least once during follow-up.

In patients who went into remission, there was no clear association with potency of immunosuppression (Table III). While more patients who went into remission received hydroxychloroquine (6/9) and fewer received rituximab (0/9), suggesting that they had milder disease, 2/9 required cyclophosphamide and almost half (4/9, 44%) were prescribed IVIG. The indication for cyclophosphamide in one patient was treatment-refractory multisystem disease (progressive ILD, skin, and joint involvement) and in the second patient was progressive lung fibrosis. Both patients received cyclophosphamide >10 years ago (in 2010 and 2011, respectively). Combination therapy was equally likely in remission and non-remission groups, with a median number of 3 concurrent medications throughout follow-up. Patients who went into remission had a similar time interval between DM symptom onset and first medication prescribed (median 0.25 years *vs*. 0.25 years), and none of them required any immunosuppressive treatment for the duration of remission.

*Baseline and longitudinal anti-MDA5 antibody titres and association with disease trajectory*

There was no association between anti-MDA5 antibody levels measured by ELISA at baseline (first collected serum in our cohort) and clinical remission (median anti-MDA5 antibody levels 139 units *vs*. 140 units, respectively; $p$=0.82). The median disease duration at the time of the anti-MDA5 antibody assay was similar in both remission and non-remission groups (median 1.4 years in non-remission group *vs*. 1.2 years in remission group). While the number of patients who died was small (n=5), there was a slight trend towards higher baseline anti-MDA5 antibody levels in those who died compared to those who did not (median anti-MDA5 antibody levels were 148 units *vs*. 137 units, respectively; $p$=0.02). In those 5 patients who died, the disease duration was similar in the sera used for anti-MDA5 antibody assay (median 1.5 years in the group who died *vs*. 1.3 years in those who did not).

Of the 52 patients, 23 (44%) had >1 longitudinal serum sample. The majority had a decrease in anti-MDA5 antibody levels (assayed by ELISA) over follow-up (Supplementary Fig. S1). In two patients, anti-MDA5 antibody levels dropped to undetectable over time. The remainder of the patients had persistently positive levels. Neither patient with negative conversion of anti-MDA5 autoantibodies achieved clinical remission, although both were on minimal levels of immunosuppression due to patient preference. Of the 9 patients who went into remission, 4 had longitudinal anti-MDA5 antibody levels assayed; the relationship of these to time of clinical remission is shown in Supplementary Figure S2.

**Table III.** Exposure (ever/never) to individual immunosuppressive and immunomodulatory agents throughout follow-up.

| Medication exposure (ever/never) | Total n=51 | Chronic n=42 | Remission n=9 | $p$-value |
|---|---|---|---|---|
| Methotrexate | 43% | 43% | 44% | 1.00 |
| Mycophenolate | 71% | 69% | 78% | 0.71 |
| Azathioprine | 51% | 50% | 56% | 1.00 |
| Rituximab | 31% | 38% | 0% | 0.04 |
| Hydroxychloroquine | 51% | 48% | 67% | 0.47 |
| IVIG | 45% | 45% | 44% | 1.00 |
| Corticosteroids | 94% | 95% | 89% | 0.45 |
| Tacrolimus | 18% | 19% | 11% | 1.00 |
| Cyclophosphamide | 6% | 2% | 22% | 0.08 |
| TNF inhibitor | 12% | 12% | 11% | 1.00 |

IVIG: intravenous immunoglobulin; TNF: tumour-necrosis factor.

## Discussion

Anti-MDA5 antibody-positive DM is a distinct entity amongst IIM, well known for the presence of unique cutaneous features and the high risk for RP-ILD with poor prognosis. Originally described in Japan, the majority of reports stem from Asian countries (Japan and China) (3, 8-17); to date, there is limited information about the prognosis of the disease in North America, where the majority of patients are White and Black (18, 19). In the current study, we have reported the clinical features and long-term prognosis of a large, single centre adult anti-MDA5-positive North American DM cohort. Approximately 20% of patients referred to our tertiary care centre and enrolled in our cohort study experienced clinical remission after a median disease duration of 4 years.

Few studies have examined the subgroup of adult anti-MDA5-positive DM that achieve clinical remission defined by continued clinical stability after discontinuation of all immunosuppression. In a Canadian cohort of 21 anti-MDA5-positive DM patients (15 of whom were of Asian race/ethnicity), three were deemed to have 'inactive disease', although it was not explicitly stated whether they were able to taper completely off immunosuppressant medications (19). Yang *et al*. used hierarchical clustering analysis to define clinical characteristics that were associated with better prognosis (young age, myalgias, serum ferritin), although they did not examine clinical remission in their cohort (20). Muro *et al*. reported a cohort of 31 Japanese an-

ti-MDA5-positive DM patients, 10 of whom had available longitudinal sera from periods of both active disease and remission (11). After a follow-up period ranging from 5-16 years, 6/10 patients achieved drug-free remission, and all 6 patients demonstrated disappearance of anti-MDA5 autoantibodies (11). Notably, in our cohort two patients who did change from positive to negative anti-MDA5 antibody levels were still taking therapeutic agents for myositis. Furthermore, in our cohort, baseline anti-MDA5 levels did not predict long-term clinical remission.

Interestingly, most data on remission in anti-MDA5-positive DM comes from juvenile DM cohorts, where the percentage of patients experiencing remission has been reported to be as high as 27-29% in both European and Asian populations(15, 21, 22). Given the severe prognosis of adult anti-MDA5-positive RP-ILD, most of the studies have focused instead on short-term mortality and associated parameters that would allow for early intervention and reversal of an adverse short-term outcome. Additionally, we suspect the scarcity of data on adult remission reflects the nature of longitudinal follow-up. That is, adults control the decision to stop returning to clinic when they are feeling better and no longer require prescription medications. Supporting this theory, in our study, 5 of 9 patients achieving clinical remission did so after their last in-person clinic visit, and were only discovered upon contacting the patient as part of this study. A major strength of our study is the comprehensive follow-up: 51/52 patients were either still followed in clinic or able to be contacted via telephone for a research interview.

Anti-Jo-1 antisynthetase syndrome is commonly associated with the development of lung disease and relatively good prognosis (23-26). In these cases, ILD tends to be stable with appropriate treatment and survival reaches 75% at 10 years (24). Interestingly, we found that anti-Jo-1-positive IIM patients had similar rates of remission (14% *vs*. 18%) and mortality (14% *vs*. 10%) compared to those with anti-MDA5-positive DM matched for disease duration. Our data suggest that while anti-MDA5-positive DM can have a dramatic presentation and potentially require a more aggressive immunosuppressive treatment regimen, these patients may have long-term survivals that are comparable with antisynthetase syndrome patients. While Asian cohorts display a higher long-term mortality than our cohort (9, 16), Isoda *et al*. demonstrated analogous long term mortality at 2 years amongst antisynthetase syndrome patients (27).

Asian cohorts are associated with more aggressive manifestations of anti-MDA5 DM and worse prognosis. In US cohorts, Black patients are disproportionately affected by IIM, have higher rates of ILD, more severe disease and worse prognosis (28-30). Therefore, we hypothesised that Black race could similarly be a risk factor for severity of ILD and mortality. However, there was no significant difference in clinical manifestations between Whites and Blacks, except for younger age at presentation and higher levels of CPK, which could be attributed to baseline difference of CPK amongst different races.

While The International Myositis Assessment & Clinical Studies Group (IMACS) has published a consensus definition of remission, "A ≥6 month continuous period with no evidence of disease activity while not receiving any myositis therapy" (31), we have elected to define remission with a longer required duration (≥12 months) given that several of the patients contacted were no longer followed in our clinic and lived at a great distance, and thus could not return easily for an in-person evaluation. Of note, using the IMACS definition would have resulted in identical results, as no patient experienced drug-free remission of >6 but <12 months duration. A limitation of this study is that our definition of remission is largely dependent on patients' subjective experience.

One of the major limitations of our study is the inherent referral bias and selection bias of our anti-MDA5-positive DM. Our low mortality likely reflects the fact that patients who presented with RP-ILD were less likely to survive to enter our outpatient longitudinal cohort study. In addition, another limitation is the retrospective nature of the study and a relatively short follow-up duration (3.5 years), and thus it is possible some patients were not followed long enough to allow for tapering of the immunosuppressive regimen. Finally, although higher KL-6 or ferritin levels have been shown to be associated with higher mortality (32) and declining levels of each are associated with response to therapy (17), we do not routinely ascertain levels of these laboratory studies in our patients. Thus, we could not comment on the potential usefulness of such markers in our population.

We have reported the clinical features and long-term prognosis of a large, single centre adult anti-MDA5-positive DM North American cohort. Approximately 20% of patients referred to our tertiary care centre experienced sustained clinical remission after a median disease duration of 4 years. No demographic, serologic, or clinical features were significantly associated with long-term remission.

**Competing interests**

E. Tiniakou has been a consultant for Horizon Therapeutics.

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L. Christopher-Stine has served on advisory boards as a consultant for Janssen, Boehringer-Ingelheim, Mallinckrodt, EMD Serono, Priovant, Pfizer, ArgenX, Horizon Therapeutics and Steritas. She received research support from Pfizer, Corbus, Janssen, Horizon Therapeutics and Kezar.

The other authors have declared no competing interests.

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