Clinical Advances in Dermatomyositis Following the Discovery of Anti-MDA5 Antibodies: Implications for Diagnosis and Disease Understanding

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Abstract

Knowledge about clinically amyopathic dermatomyositis has exploded in the last two decades, especially after the discovery of anti-MDA5 Ab. The disease's likely genesis and pathophysiological processes have been studied in a number of scientific and epidemiological studies. Thanks to a slew of new large-scale cohort studies, the clinical characteristics of MDA5+ DM may be better identified. In addition, several prognostic indicators have been discovered, such as respiratory physiology measures and serum biomarkers, which have helped to enhance risk categorization in clinical practice and restrict the design of future clinical studies. Quantitative evaluation of pulmonary HRCT data may be the trend of imaging testing in MDA5+ DM-ILD. The current standard of treatment for MDA5+ DM-ILD is "triple treatment" with JAK inhibitors, which has been proven in recent trials to significantly improve the survival of early-stage patients. Total mortality in this incurable disease, however, is still shockingly high, especially in advanced-stage patients. There is still a pressing need for a more effective and well-evidenced treatment approach for MDA5+ DM-ILD.

Introduction

Idiopathic inflammatory myopathy (IIM) with anti-melanoma differentiation-associated gene 5–positive dermatomyositis (MDA5+ DM) is a rare but unique subtype of idiopathic inflammatory myopathy (IIM) that has been identified globally, but primarily in East Asia. Adult MDA5+ DM is characterized by typical dermatomyositis rashes, amyopathic or hypomyopathic muscle involvement, and substantial interstitial lung disease (ILD), which often progresses rapidly. MDA5+ DM-ILD is a difficult illness with a significant fatality rate.

MDA5+ DM Terminology and Classification

The acknowledgment of this distinct clinical entity has progressed over the last two decades and may be separated into two phases. The discovery of the disease's serological signature, anti-MDA5 autoAb (1, 2), was a watershed moment. The terminology was clinically amyopathic dermatomyositis (CADM), proposed by dermatologists (3) and largely accepted in the first decade, referred to as the pre-MDA5 period. According to professional opinion, the nomenclature has progressively been modified to MDA5+ DM in the post-MDA5 decade (4). In fact, over 87 percent of our multi-centered MDA5+ DM-ILD cohort of more than 300 patients met Sontheimer's preliminary CADM criteria, whereas roughly 78 percent of CADM-ILD patients recruited in another large single-center cohort tested positive for anti-MDA5 (5). As a result, there is a lot of overlap between these two terminologies, especially when it comes to ILD.

The MDA5+ DM categorization criteria are being upgraded at the same time as the changeover. The latest European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria for IIM are data-driven, in contrast to Sontheimer's criteria, which were narrative in character (6). Unfortunately, relatively minimal myositis-specific autoAbs (MSAs) data was incorporated into the algorithm. The recommended requirements of the 239th ENMC, on the other hand, are more appropriate for MDA5+ DM (4). Patients with classic DM rashes (Gottron's papules or Gottron's sign and heliotrope rash), as well as either "interface dermatitis" skin pathology or indications of myositis or an MSA, are likely to be diagnosed with DM. In other words, the presence of classic DM rashes plus a positive anti-MDA5 antibody is sufficient to diagnose MDA5+ DM.

Anti-MDA5 autoAb's pathognomonic value for MDA5+ DM necessitates high accuracy for several tests. Although the immunoprecipitation assay is regarded as the "gold standard" for MSAs, its use is restricted for practical reasons (1). The line-blotting approach has been verified, with good agreement with immunoprecipitation results for anti-MDA5 in particular (7). For anti-MDA5 testing, we employed line-blots in conjunction with an independent enzyme-linked immunosorbent assay (ELISA) at our facility (2, 8). Our experience has shown that two separate anti-MDA5 tests are required, especially when the readout of one assay is unknown.

Rapid progressive ILD (RPILD) has long been thought to be a critical feature of adult MDA5+ DM that is linked to poor prognosis (9). The frequency of ILD in MDA5+ DM has been reported to range from 50 to 100 percent (10,11,12). The disparity is most likely due to referral bias and demographic disparity. Nonetheless, a three-dimensional (derm, muscle, and ILD) paradigm for allocating distinct IIMs was developed to get the full picture by putting this unique entity into the context of other IIMs. RPILD is a phrase used in MDA5+ DM that refers to people who have quantifiable advancement within a short amount of time from the beginning of ILD, although there is no consensus on what it means. We propose that RPILD in MDA5+ DM be defined as either worsening of dyspnea and CT progression within 1 month, or deterioration to respiratory failure within 3 months since the onset of respiratory symptoms (1, 11), referring to ATS's terminology for progressive disease in idiopathic pulmonary fibrosis (IPF) (13). This criteria might apply to the majority of prior studies, with RP-ILD incidence ranging from 38 to 71 percent (5, 11, 12, 14,15,16,17).

MDA5+ DM Pathogenesis and Etiology

The etiology and pathophysiology of MDA5+ DM, like other kinds of DM, are unclear. In most cases, the illness is caused by genetically predisposed people being exposed to environmental causes. Environmental risk factors for MDA5+ DM have been discovered in just a few studies. MDA5, which is encoded by the IFIH1 gene, is a retinoic acid-inducible gene I (RIG-I)-like receptor (RLR) that serves as a crucial protein sensor for viral dsRNA. Picornaviruses including hepatitis A, coxsackie B, enteroviruses, and rhinoviruses can activate MDA5 and cause it to produce type I IFN (IFN and IFN) and other inflammatory cytokines that aid in the antiviral response. Overactivation of the type I IFN pathway has been linked to the development of autoinflammatory disorders (18). As a result, it was suggested that viral infections might be a catalyst for the development of MDA5+ DM. According to a single-center research from Japan, the majority of MDA5+ DM patients lived outside of cities and near a large river (19). A larger cohort found that MDA5+ DM-ILD occurred primarily in persons living near the shoreline, especially freshwater, from October to March the following year, implying an environmental effect (20).

Although there was no correlation between anti-MDA5 and HLA allele region in Caucasians, HLA-DRB * 01:01/* 04:05 was vulnerable to MDA5+ DM in the Japanese population (4, 21, 22). A splicing variation of the WDYF4 gene was discovered in CADM patients in a recent GWAS investigation, which might augment MDA5-induced apoptosis via activation of NK-B (23). Transcriptome analysis revealed more about the disease's pathogenesis. The gene expression profile of MDA5+ DM in the skin was characterized by Charles et al. The study found that MAD5+ DM skin involvement was linked to immune cell activation and infiltration, as well as upregulation of the type I IFN signature at the molecular level. IFN-, which is exclusively released by keratinocytes, was exclusively enhanced in anti-MDA5+ skin, suggesting that it may have a role in the pathogenesis of its skin lesions (24). Mx1, a type I IFN signature gene, was highly elevated in skin lesions from MAD5+ DM, dispersed in blood vessels, and disseminated to the deep dermis, implying an IFNopathy-related vasculopathy (25), according to a previous report by Nobuyuki et al.

Muscle involvement in anti-MDA5+ individuals is often modest (amyopathic); nonetheless, MDA5+ DM in muscle tissue exhibited the same IFN profile as MDA5 DM. Interferon-induced genes like ISG15, for example, were shown to be substantially expressed in RNAseq of muscle biopsies from MDA5+ DM (26, 27). IFN, ferritin, and IL-18 blood levels were considerably greater in MDA5+ DM with RPILD, according to Japanese researchers (28). A Chinese study found an elevated interferon gene signature in MDA5+ DM patients' PBMC and skin biopsies.More crucially, the presence of a high IFN gene profile was found to be strongly linked to BAFF expression. The concentrations of KL-6, a lung damage indicator, were in line with BAFF levels (29). Despite the dearth of mechanistic evidence, the type I IFN pathway is expected to play a key role in the pathogenesis of MDA5+ DM.

Another feature of MDA5+ DM-ILD is hyperinflammation, as demonstrated by severe hyperferritinemia. Serum cytokine patterns in this condition have been studied in a number of investigations. IL-8 levels were substantially greater in MDA5+ ILD than in anti-tRNA synthetase (ARS) + ILD, according to one research (30), although IL-6, TNF-a, and IP-10 levels were high in both groups. In another investigation, serum IL-15 was shown to be a promising biomarker in MDA5+ ADM-ILD patients. IL-15 levels were significantly higher in non-survivors than in survivors before treatment, suggesting that it might be used as a prognostic marker (31). Another study looked at the relationship between serum cytokine levels and lung high-resolution computed tomography (HRCT) patterns in MDA5+ DM-ILD patients. Patients with RPILD had substantially greater levels of IFN-, IL-1, and IL-12, and serum IFN-associated with ground-glass opacity (GGO) score, but serum IL-1 levels were linked negatively with fibrosis score. Furthermore, the lungs and hilar lymph nodes of DM with RPILD demonstrated high IFN-related immune responses (32). The blood cytokine/chemokine levels of Chinese DM/CADM patients were examined by Chen et al (with 50 percent positive for anti-MDA5). Anti-MDA5 levels were linked to IL-6 and IL-18 levels in the blood (33). The cytokine profile in MDA5+ DM-ILD is likely to be dynamic at different phases of illness among various individuals because there is no common pattern.

MDA5+ DM-ILD Clinical Characteristics and Outcome

MDA5+ DM-ILD has been seen in a variety of ethnic groups, with a preference for Japanese and Chinese (5, 15, 17, 34,35,36). The majority of patients are female (two-thirds), with a median age of 50. By definition, dermatomyositis-specific rashes, such as heliotrope rash, Gottron's papules, or signs, are pathognomonic. Mechanic hand and cutaneous ulcerations affect 20 to 30 percent of patients. Fever, arthralgia, and myalgia are typical constitutional and musculoskeletal complaints. The majority belong to the CADM phenotype. Hoarseness or sore throat, as well as dysphagia, are typical symptoms. Malignancy is infrequent in MDA5+ DM-ILD (incidence 5%), due to a negative connection between ILD and MDA5+ DM-ILD (17, 37). Cardiovascular problems (such as new-onset atrial fibrillation or an increase in cardiac troponin) and spontaneous intramuscular bleeding are also uncommon.

MDA5+ DM-ILD or CADM-ILD patients have a bad prognosis. The majority of deaths occur within the first half year of the disease because of persistent RPILD despite rigorous immunosuppressive therapy, resulting in a high 6-month mortality reported in early cohort studies ranging from 33 to 66 percent (17, 36, 38, 39). Despite progress in prompt diagnosis and more efficient care, 6-month mortality in our large multi-center Chinese MDA5+ DM-ILD cohort is still over 40%. Appropriate stratification of individuals based on predictive risk variables will be a critical step forward in aligning diverse research and limiting future clinical trial design.

MDA5+ DM-ILD Staging Using Respiratory Physiology

Recently, a five-component composite risk score dubbed the "FLAIR score" was suggested to predict mortality in ADM-ILD, which includes ferritin level, lactate dehydrogenase level, semi-quantitative anti-MDA5 antibody grade, HRCT imaging score, and RPILD/non-RPILD. According to the FLAIR score, ADM patients might be divided into three risk groups (low, medium, and high). These results were generated from an internal validation of a large-scale Chinese single-center cohort (n = 207). Unfortunately, the variability of this sample was demonstrated by the fact that 22% of patients (n = 45) were anti-MDA5 antibody negative. Furthermore, due to the retrospective design, the pulmonary function and structural evaluation (HRCT score, see Sect. 5) was unsatisfactory (5).

To return to the beginning, respiratory physiological characteristics are critical for the prognosis of ILD, independent of the cause. Indeed, in various small-sample MDA5+ DM/CADM investigations, several characteristics, such as lower PaO2 and larger alveolar-arterial oxygen differential (AaDO2), have been linked to the development of RPILD and poor prognosis (12, 36, 40). The baseline forced vital capacity (FVC) percent was identified and verified as the most important prognostic predictor to predict 6-month all-cause mortality based on our multi-center MDA5+ DM-ILD data.

The appropriate FVC percent cutoff value of 50% may considerably separate patients into two danger phases, namely early-stage (FVC percent 50%) with a 15% mortality rate and advanced-stage (FVC percent 50% or unable to do PFTs) with a 70% mortality rate. This simple, non-redundant categorical predictor based on FVC percent is useful for risk stratification in clinical practice and may aid with cohort enrichment for future trials.

MDA5+ DM-ILD pulmonary HRCT assessment

Pulmonary HRCT is a common imaging technique used to diagnose ILD. Pneumomediastinum (PNM), a potentially fatal consequence in MDA5+ DM-ILD, has long been recognized as a distinguishing imaging characteristic that reflects disease severity. Despite receiving rigorous immunosuppressive treatments, individuals with PNM had a substantially poorer survival rate in a Japanese research including 31 patients with MDA5+ DM. Prior to treatment, the HRCT score in the PNM group was likewise lower (41).

In another Chinese research, 20 out of 133 (15%) patients were diagnosed with PNM, with a 1-year survival rate of just 40% in this sample. The use of a noninvasive positive pressure ventilator (NPPV) has been shown to worsen PNM outcomes (42). PNM, on the other hand, may not be sensitive enough at baseline to aid prognosis prediction.

Initially, the radiological features of MDA5+ DM-ILD were documented in a few modest investigations. According to Hozumi et al., the most distinguishing HRCT pattern of MDA5+ DM was "unclassifiable," which was a combination of consolidation and GGO with reticulation pattern not characteristic for pure nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), or ordinary interstitial pneumonia (UIP) (43). In addition, for the assessment of MDA5+ DM-ILD, a semi-quantitative HRCT grading system taken from IPF evaluation was used. This score was validated as an independent risk factor for 1-year death by Zou et al. (44). The overall score was calculated by weighing three factors: GGO, consolidation, and fibrosis (including traction bronchiectasis and honeycombing alterations). Unfortunately, in this scoring technique, the fibrosis components were significantly weighted, which does not appear to be a great fit in MDA5+ DM-ILD. A Japanese group presented a reduced scoring technique in which just the GGO and fibrosis components were weighted, but the consolidation characteristic was ignored (40, 41). Indeed, a recent larger-scale investigation in China found that among patients with MDA5+ DM, the OP-like pattern was the most common radiological type (45). Furthermore, lower zone consolidation has been shown to be linked to RPILD (45, 46). The key observation in MDA5+ DM-RPILD pathologically comparable to diffuse alveolar damage (DAD) was also identified as aperilobular opacity converting to consolidation (47, 48).

Unbiased quantitative imaging evaluation for MDA5+ DM-ILD using an artificial intelligence (AI) algorithm is very likely to become a reality. More precise imaging evaluation of MDA5+ DM-ILD is still pending till then. The representative symmetrically distributed GGO and consolidation patterns, with a "gravity gradient" predisposition for the consolidation in particular to the lower portion of the lungs.

MDA5+ DM-ILD biomarkers

MDA5+ DM-ILD has been linked to a number of biomarkers. Several studies have looked at the prognosis utility of anti-MDA5 Ab titers as well as their diagnostic utility.In MDA5+ DM-ILD, baseline serum anti-MDA5 Ab titers determined by ELISA were not shown to be a significant risk factor for death (49). The significance of anti-MDA5 Ab titer fluctuations over time was debated. Anti-MDA5Ab titer considerably decreased following treatment in survivors, but non-survivors had high levels of anti-MDA5 Ab and ferritin, showing that anti-MDA5 Ab titer is beneficial for evaluating treatment response (36). However, in a separate research of 24 patients, an initial drop in anti-MDA5 Ab titer following immunosuppressive therapy was detected in the majority of patients, regardless of whether they were alive or dead, showing that it is insufficient for predicting short-term treatment response (34).

Nonetheless, among patients who were in remission and had low anti-MDA5 Ab titers, a rise in anti-MDA5 Ab levels was linked to illness relapse, suggesting that anti-MDA5 Ab titer might be a valuable indicator for monitoring disease activity and predicting illness flare in long-term follow-up (50, 51). An intriguing research looked at the coexistence of myositis-associated autoantibodies (MAAs, which include anti-nuclear antibodies, anti-cyclic citrullinated peptide antibodies, anti-SSA antibodies, and anti-SSB antibodies) in 24 MDA5+ CADM patients (37.5 percent had at least one MAA). Patients with concomitant MAAs had a decreased probability of developing RPILD, a better response to immunosuppressive therapy, and a lower death rate than those who did not have MAAs (14). Coexisting anti-Ro52 was more common in RPILD in a North American case series with MDA5+ DM (n = 21) (16).

Apart from autoantibodies, ferritin is a well-established serum biomarker for MDA5+ DM-ILD, with reported cutoff values ranging from 450 to 2000 ng/ml (36, 40, 53, 54), and is related to the severity of ILD (52) as well as prognosis. Lactate dehydrogenase (LDH) is also linked to the disease activity of diabetic individuals, particularly those with normal CK levels. Serum LDH was considerably greater in DM-RPILD individuals than in DM with chronic ILD (55). The likelihood of lung function impairment is increased in MDA5 DM-ILD patients when high levels of LDH are accompanied by anti-MDA5 antibodies (56). According to a recent cohort research, serum LDH in MDA5+ DM-ILD survivors was considerably lower than in nonsurvivors, and LDH (> 355 units/L) might be an independent high-risk marker for poor outcome (5). Damaged bronchial epithelium and regenerative type II alveolar cells secrete Krebs von den Lungen-6 (KL-6), a mucin-like high molecular glycoprotein (57). Patients with DM-ILD had considerably greater serum KL-6 concentrations than those without ILD. With the development or improvement of ILD, the value of serum KL-6 fluctuates (58). According to recent research, serum KL-6 levels in MDA5+ DM-ILD patients were considerably greater than in MDA5 DM-ILD and healthy controls. Furthermore, the level of KL-6 was linked to the HRCT score. Patients with high levels of KL-6 have a considerably poorer one-year survival rate than MDA5+ DM-ILD patients with low levels of KL-6. The blood KL-6 level reduced dramatically while the illness was under control (59).

In active MDA5+ DM-ILD, peripheral lymphocytopenia is a common and straightforward finding. Lower CD3+ T cell numbers have also been linked to a lower chance of survival (15). These findings, however, might potentially be the outcome of intensive immunosuppressive therapy. Immunophenotyping of various lymphocyte groups is required. Wang et al. (61) recently discovered that a distinct population of peripheral T cells, namely CD4+ CXCR4+ T cells, was related to IIM-ILD, particularly MDA5+ DM-ILD. The percentage of CD4+ CXCR4+ T cells was linked to the severity of the HRCT score as well as pulmonary function deficits (FVC and DLco) and, as a result, death. CD4+CXCR4+ T cells from MDA5+ DM-ILD patients were found to be capable of boosting pulmonary fibroblast proliferation via an IL-21/JAK-dependent pathway.

Another potentially mechanistic biomarker for MDA5+ DM-ILD is IL-15. After a viral infection, IL-15 is primarily released by epithelial cells, skeletal muscle cells, macrophages, and dendritic cells. It can then trigger the activation of natural killer cells, which is part of the antiviral immune response. Acute lung injury might be a side effect (61). IL-15 has been found to be expressed not only in the muscles of diabetic patients, but also in the lung tissue of DM-ILD patients (62). The level of IL-15 in the blood was found to be considerably higher in MDA5+ DM-RPILD patients and was linked to poor survival (63).

Serum chitinase-3-like-1 protein (YKL-40) (15), IL-6 (64), and IFN-(28) are examples of biomarkers that may give further information.

Medications

For MDA5+ DM-ILD, early diagnosis, correct risk stratification, and adequate therapy are critical for a positive result. The existing therapies, on the other hand, are mostly empirical and not evidence-based (65). Due to the disease's rarity and severity, only a few prospective open-label studies have been done.

The Japan Protocol on "Triple Therapy"

Because this is such a difficult illness, combining traditional immunosuppressants makes sense. Based on a multicenter prospective trial (39), Japanese colleagues proposed the "triple treatment," which is an upfront combination of high-dose glucocorticoids, tacrolimus, and intravenous cyclophosphamide. The "triple therapy" group (n = 29) had a 6-month survival rate of 89 percent, compared to 33 percent in the "10-year-older" historical step-up treatment group (n = 15) (p 0.001). However, the baseline average FVC percent was 78.8%, indicating that the majority of patients were in the early stages of their disease, as determined by our risk assessment, and hence more likely to react to therapy. There is a scarcity of evidence to back up the efficacy of "triple treatment" in advanced-stage patients, i.e., those with a baseline FVC percent of less than 50%. Furthermore, this regimen had a number of safety problems, including opportunistic infection (3 CMV reactivation, 2 PJP, and 2 sepsis episodes).

"The Protocol of JAKi": The Protocol of Shanghai

In the case of MDA5+ ADM-ILD with IFNopathy and hyper-inflammation, a JAK inhibitor has emerged as a promising therapy option. In a recent single-center open-labeled trial, we discovered that tofacitinib, at a dose of 5 mg twice daily, combined with glucocorticoids, improved the survival of early-stage MDA5+ ADM-ILD patients (consecutive eligible patients with an inclusion criterion of FVC percent 50% and an average baseline FVC percent of 73.4 percent, n = 18) compared to matched historical controversies. This protocol's safety profile in early-stage illness is similarly excellent. Although it is unreasonable to compare the efficacy of "JAKi's regimen" to "triple therapy," an observational research from Japan found that switching "triple treatment" to tofacitinib as a rescue method for refractory high-risk MDA5+ ADM-ILD patients might increase survival (mortality 40% versus 100%) (54). More research into the treatment based on "JAKi's regimen" in advanced-stage illness is needed.

Plasmapheresis and Other Biologic Agents

Other biologic medicines have been reported to have had positive experiences in case reports or series (67,68,69). According to one case study, 15 of 28 RPILD patients reacted to rituximab (RTX, anti-CD20 monoclonal antibody), the majority of whom were unresponsive to conventional therapy (16). In a small case series (n = 4) with MDA5+ CADM-ILD, basiliximab, an anti-CD25/sIL-2R monoclonal antibody, combined with prednisone and cyclosporine, showed probable effectiveness (68).

Six instances of patients unresponsive to extensive immunosuppressive treatment were effectively treated by plasmapheresis as an additional treatment in a recent Japanese trial, with four adverse effects including anaphylactic shock and catheter infection (70). Because transfusion-induced acute lung damage has been documented following plasma exchange in MDA5+ DM-ILD (71), caution should be used. There was insufficient evidence to back up polymyxin B hemoperfusion's effectiveness. Even with the addition of polymyxin B hemoperfusion on the basis of "triple therapy," 9 out of 10 refractory patients with MDA5+ CADM-RPILD finally perished, according to retrospective research (72).

Drugs to treat fibrosis and other forms of supportive care

In a prior open-label trial (73), we found that adding pirfenidone to standard immunosuppressive therapy at a target dosage of 1800 mg/day did not improve survival over traditional immunosuppression alone. However, as compared to matched historical controls, the pirfenidone add-on was only advantageous for patients with subacute CADM-ILD (disease duration 3–6 months) according to an exploratory sub-analysis. Direct pirfenidone-related significant side effects, such as liver function abnormalities, rash, and diarrhea, were found in 10% of patients.

Several case reports and series have shown that MDA5+ DM-RPILD patients can have a successful lung transplant (74, 75). Kun Huang et colleagues. reported that all four patients who had failed to react to immunosuppressive medication and had started pretransplant extracorporeal membrane oxygenation (ECMO) assistance as bridging survived at least 12 months following bilateral lung transplantation in a recent case study (75).

Because opportunistic infections are frequent in MDA5+ DM-ILD patients, especially following immunosuppressive therapy, In MDA5+ DM-ILD, Pneumocystis jirovecii pneumonia (PJP), cytomegalovirus (CMV), and invasive fungal infection were all common (39). The threshold for prophylactic and pre-emptive therapy is low; nonetheless, there are no evidence-based guidelines.

Conclusion

During the last two decades, knowledge of clinically amyopathic dermatomyositis has grown dramatically, notably after the discovery of anti-MDA5 Ab. Several scientific and epidemiological studies have been conducted to investigate the disease's likely origin and pathophysiology processes.The clinical features of MDA5+ DM might be more fully defined thanks to numerous recent large-scale cohort investigations. Furthermore, various prognostic indicators, such as respiratory physiology parameters and serum biomarkers, have been found, which considerably improve risk classification in clinical practice and help to limit the design of future clinical trials.

The trend of imaging examination in MDA5+ DM-ILD may be quantitative assessment of pulmonary HRCT results. The current standard of care for MDA5+ DM-ILD is "triple therapy" and JAK inhibitor-based therapy, which has been shown to considerably enhance the survival of early-stage patients in recent trials. However, total mortality in this incurable disease remains alarmingly high, particularly in advanced-stage patients. In MDA5+ DM-ILD, there is still a pressing need for a more effective and well-evidenced treatment plan.

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