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Advances Toward Precision Medicine in Juvenile Dermatomyositis

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Abstract

Purpose of Review We seek to provide a summary of the recent advances in juvenile dermatomyositis (JDM) that are moving the field toward precision care and personalized medicine for this uncommon condition.

Recent Findings There has been a recent international focus on developing uniform classification, disease monitoring, and treatment for juvenile dermatomyositis. In addition, there has been a steady development of translational studies to determine the genetic determinants, transcriptomic profiles, and immune cell phenotypes in JDM.

Summary Recent work toward standardization of disease classification, monitoring, and assessments together with advances in science, technology, and computing will facilitate the advancement toward true precision and personalized medicine in juvenile dermatomyositis in the near future.

Keywords Juvenile dermatomyositis · Idiopathic inflammatory myopathies · Translational research · Precision medicine

Introduction

Juvenile dermatomyositis (JDM) is a systemic immune-mediated vasculopathy of children, characterized by pathognomonic rashes and muscle weakness, but can also involve other vital organ systems [1, 2]. Historically, without treatment, mortality was over 30%, but with modern day therapies, this has improved and now estimated to be less than 3% [3]. However, the majority of JDM patients continue to have chronic morbidity and damage long into their disease course [4–7], so there remains a vital need for progress in the treatment and cure of JDM. To achieve this end, the field of JDM research and care has been working to improve the identification of the condition, assessment and monitoring of disease activity, and treatment approaches, in addition to working to understanding of the risk factors, pathogenesis, and biology of this rare condition.

Furthermore, innovations in technology and computing power are driving the medical field toward the age of personalized medicine. This movement has applications across many specialties but is particularly exciting in the field of rheumatology, especially in conditions like JDM, where diseases are multifactorial and result from a combination of numerous known and unknown genetic variants and environmental exposures. In JDM, patients have heterogeneous clinical presentations with a wide range of clinical symptoms, disease severity, and clinical course. These observations have spurred a body of research to characterize the disease and subtypes of disease both clinically and at the molecular level in efforts to improve care for individual patients.

In this review, we outline recent developments in understanding risk of factors related to JDM and focus on the development of harmonized classification and monitoring tools in JDM, as well as review of recent translational studies.

Risk Factors and Expression of Disease

Some unique risk factors have been identified in various studies over the past several years, which expand our understanding of JDM risk factors and disease expression.

Based on an online patient survey of US and Canadian JDM and adult DM patients (n = 164 and 46, respectively), who were ≥ 1 year from diagnosis and diagnosed between 1980 and 2011, environmental factors associated with disease flare were described [8]. Investigators found environmental exposures to be associated with disease flares, which included sun exposure, medication use (NSAIDs, blood pressure medications, and medications for mood), and infections (urinary

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tract infections and gastroenteritis) within 6 months of flare compared with patients who did not flare. However, only sun exposure and NSAID use were found to be significant in a multivariable analysis. Whether these survey findings are clinically meaningful will require future studies and testing.

The Childhood Myositis Heterogeneity Study Group, which enrolled 365 patients from the USA and Canada, found an association between myositis autoantibodies, early clinical features, and environmental exposures at illness onset that were able to predict long-term disease course in JDM [9]. Myositis specific and associated antibodies, in particular anti-p155/140, and a number of early clinical features and environmental exposures (UV exposure and infections) prior to the diagnosis of JDM, were associated with a chronic course.

Some interesting analyses have also recently come from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) legacy registry, which recruited pediatric patients from 55 centers across North America between 2010 and 2015, including over 650 subjects with juvenile dermatomyositis. CARRA is a North America–based organization of pediatric rheumatologists and related providers founded in 2002, with over 500 members that seek to better understand and treat pediatric rheumatic diseases. From this registry, clinical phenotypes and biologic treatment in JDM-associated calcinosis were analyzed where 13% (84 of 631 patients) had a history of previous or current calcinosis. Calcinosis was found more often in patients with prolonged active disease, severe disease, and specific clinical features including lipodystrophy and joint contractures. The authors also found that patients with calcinosis were treated with more aggressive therapy, including IVIG and rituximab, which may reflect chronically active or refractory disease in this patient population [10].

A second analysis from the CARRA legacy registry found that minority race and income were associated with worse disease outcomes in JDM [11]. To understand if these differences are primarily related to health disparities versus differences in disease severity and expression in patients from different races requires additional study. A subsequent analysis of this registry transposed with UV index data from the National Oceanic and Atmospheric Administration (NOAA)/Climate Prediction Center found differences in calcinosis risk based on UV index exposure; while higher UV exposure was associated with an increased risk of calcinosis in white JDM patients, lower UV exposure was associated with this increased risk of calcinosis in the African-American patients [12]. This suggest that UV radiation may play a differential a role in the clinical course of JDM according to race, and additional future consideration is needed.

Standardization

Standardization of assessment and care is required in order to catalogue and comprehend heterogeneous conditions like JDM. There have been several important publications over the past several years that help us to develop a more uniform approach worldwide to help to achieve this goal and facilitate uniform diagnosis, data collection, monitoring, and treatment.

Disease Classification and Monitoring

The classification of inflammatory myopathies, including JDM, has historically been based on criteria that were developed in 1975 [13]. Updated classification criteria for adult and juvenile idiopathic inflammatory myopathies (IIMs) and their major subgroups were published in 2017 [14]. These criteria were developed through a data-driven process that included pediatric data and expertise from a broad international group of experts who care for patients with myositis. An online calculator, which provides the probability of having IIM, was developed to facilitate its acceptance and use: http://www.imm.ki.se/biostatistics/calculators/iim/. These new classification criteria were validated in a cohort of Chinese patients [15], and reported a higher sensitivity, specificity, and classification rate using the new criteria compared with the 1975 criteria.

As important as making the correct diagnosis of JDM is the ability to measure disease activity, as well as the ability to measure clinically meaningful changes in disease activity. In 2016, the ACR/EULAR criteria for minimal, moderate, and major clinical responses in JDM were developed using data-driven and expert group decision-making processes.These criteria were developed using core set measures of IMACS or PRINTO and validated with data from new cohorts and clinical trials [16]. A practical web calculator was also developed to facilitate its use: https://www.niehs.nih.gov/research/resources/imacs/response_criteria/adult.html.

Data Collection

Our ability to measure and document disease activity consistently and reliably over time is of vital importance in both clinical and research settings. Due to the variability in clinical presentation and course of JDM, no single measure can reliably capture disease activity in all patients; thus, there is an alphabet soup of recommended assessments, which include strength, skin, and functional assessment tools, as well as physician and patient global assessment of disease activity and functioning: the childhood myositis assessment scale (CMAS), manual muscle testing of 8 muscle groups (MMT-8), cutaneous assessment tool (CAT), cutaneous dermatomyositis disease area and severity index (CDASI), disease activity score (DAS), childhood health assessment questionnaire (CHAQ), and physician's and patient's global assessment on a visual analog scale (PGA) [17]. Together, in conjunction with standard laboratory assessments including muscle enzymes and autoantibodies, clinicians and researchers are able

to approximate disease activity of JDM, though there are practical constraints that may limit collection of these data types in the outpatient setting. Core sets of variables for assessment of disease activity and therapeutic response in JDM have been established by both the Pediatric Rheumatology International Trials Organization (PRINTO) and the International Myositis Assessment and Clinical Studies Group [18, 19].

To help standardize assessments and aid international collaboration, a minimal or optimal dataset has been developed through consensus [20]. This dataset has the potential to enhance collaboration among myositis specialists, which is key in studying a rare disease like JDM. This dataset will also hlep improve communication of disease assessment across countries and specialties.

Some recent work has focused on simplifying the measurements of disease activity in efforts to decrease the time needed to collect disease assessment measures. Rosina et al. sought to develop a pragmatic approach to the measurement of disease activity in JDM. With input from 8 pediatric rheumatologists, they developed and preliminarily validated a composite disease activity score called the Juvenile DermatoMyositis Activity Index (JDMAI) for the measurement of muscle and skin involvement in JDM, which includes the physician and patient PGA, muscle strength, and skin disease activity [21].

There are limitations in current approaches in any single measure of strength testing, and a hybrid measure of muscle strength (hMC) for JDM has been developed. This hypbrid measurement is an 11-item instrument, which includes the MMT-8 and the following 3 items of the CMAS: time of head lift, assessment of sit-ups, and floor rise. They found this measure to be quick to complete (less than 10 min). Prospective testing is needed in other patient populations, but this study suggests that the hMC has the potential to be used practically in routine clinical care with the added benefit of testing both strength, endurance and function [22].

Cutaneous manifestations of JDM are an important indicator of disease activity and inflammation that requires close monitoring over time. There are several skin scoring tools that are available for JDM, including the DAS and CAT, which have their own advantages and disadvantages. More recently, the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) was studies and validated in children with JDM [23]. This tool was previously validated in adults and demonstrated better responsiveness to clinical change when compared with other measures of skin disease in adult dermatomyositis. The practical utility and reliability of pediatric rheumatologist and dermatologists using the CDASI was recently confirmed. The CDASI is unique in that it assesses skin activity and damage in 15 anatomical sites, which may not be captured completely by other skin assessment tools.

Though comprehensive data collection is not practical in most general pediatric rheumatology settings, we would recommend that clinicians consider standardizing their personal clinical practice of data collection regarding muscle and skin disease activity. This will allow for more informed clinical decision-making since consistent collection of data to measure disease activity and burden in JDM is important to guide treatment recommendations.

Monitoring and Treatment

The Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) initiative has sought to identify best practices for diagnosis and treatment of patients suffering from pediatric rheumatic conditions, including JDM. Using evidence-based informed consensus, researchers developed a set of recommendations for the diagnosis and treatment of JDM with the goal of developing a standard of care for patients with JDM throughout Europe. It is a comprehensive compilation of recommendations, which includes 52 recommendations (33 on diagnosis and 19 on therapy) [24].

The JDM Committee of CARRA has developed consensus treatment plans (CTPs) for moderate JDM and more recently for patients with JDM with resistant skin disease and skin-predominant JDM. These CTPs were developed through experts consensus and are meant to reflect typical approaches in the treatment of these JDM subtypes. The goal of these CTPs are to help standardize treatment approaches and facilitate pragmatic comparative effectiveness trials to inform future best treatment practices [25]. JDM patients with resistant skin disease includes patients with persistent JDM skin rashes despite resolution of muscle involvement. Treatment plans for this JDM subtype included the addition of intravenous immunoglobulin, mycophenolate mofetil, or cyclosporin [26]. Skin-predominant JDM includes the subset of children who have the typical rash of JDM without significant weakness. Treatment plans for this JDM subtype included hydroxychloroquine, hydroxychloroquine, and methotrexate or hydroxychloroquine, methotrexate, and corticosteroids [27].

Similarly, in Germany, a JDM working group of 23 pediatric experts from the Society for Pediatric Rheumatology (GKJR) developed statements to aid in the management of moderate and severe JDM. Overall 10 statements were developed ranging from case definitions to diagnosis, baseline testing and monitoring, and treatment targets [28]. They emphasized the important concept of a treat-to-target strategy, suggesting that therapies are modified according to reaching or failing previously established targets. Overall, these guidelines align with recommendations made from both CARRA consensus treatment plans and the SHARE recommendations.

Glucocorticoids are central in the initial treatment of JDM. However, when and how to taper corticosteroids in order to limit side effects, while adequately treating the disease not standardized. PRINTO has developed a proposal for glucocorticoid tapering, based on the improvement in JDM PRINTO/ACR/EULAR core set measures from patients enrolled into

the PRINTO JDM trial [29], which may help to guide or standardize steroid tapering [30].

Learning from Translational Studies

While clinical and epidemiological studies are vital for characterizing the clinical phenotypes of JDM, translational studies to determine the genetic determinants, transcriptomic profiles, and immune cell phenotypes in JDM are needed to develop a personalized medicine approach.

Genetics: HLA and Beyond

JDM is a complex polygenic disease with several identified genetic risk factors. Genetic-wide association studies (GWAS) conducted through the Myositis Genetics Consortium (MYOGEN) have advanced our knowledge of the genetic factors associated with idiopathic inflammatory myopathies (IIM) in people of European ancestry, including JDM [31]. As is true in many autoimmune diseases, the human leukocyte antigen (HLA) region had the highest association with JDM, but the authors were able to refine a specific region of the HLA locus, known as the HLA 8.1 ancestral haplotype, as the primary genetic risk factor in Caucasians explaining virtually all the genetic risk in myositis. This genetic region is complex and comprised of several alleles, including HLA DRB1*03:01, which had the strongest association with adult DM and JDM. However, the contribution of multiple alleles from this region was required to confer the strongest risk.

In a follow-up MYOGEN study using a custom Immunochip assay, the significant association with the HLA 8.1 ancestral haplotype was confirmed and additional non-HLA variants in immune genes were identified as potentially associated with the major myositis subtypes [32]. In this study, adult DM and JDM were analyzed together and three additional non-HLA variants reached the suggested level of significance. One variant mapped to the gene GSDMB, which was particularly interesting because two variants within this gene were predicted by a software program as "potentially damaging" in terms of protein production, and several expression quantitative trait loci (eQTL) were identified near the gene suggesting possible functional implications.

Complement C4A deficiency has also been identified as a genetic risk factor in JDM both independently and more so in combination with the HLA DRB1*03:01 allele, suggesting this variant creates a permissive genetic background [33]. Evaluating copy numbers of C4A and C4B, JDM patients with lower numbers of C4A had higher complement deposition on erythrocytes and higher muscle enzymes at diagnosis. C4A deficiency has also been identified as a risk factor in systemic lupus erythematosus, and in both diseases may lead to increased immune activation through poor clearance of immune complexes, though the exact mechanism is unknown.

Because genetic studies require a tremendous samples size and JDM is a rare disease, these studies additionally highlight the excellent collaborative work that has been done in the myositis community that will be integral to advancing further understanding of the genetic factors that contribute to JDM.

Transcriptomics: Interferon Signaling Is Prominent in Target Tissues and Complex

Gene expression studies involving the target tissues and peripheral blood have laid a solid foundation for further exploration of underlying pathophysiology in JDM. Many studies have reported on the presence of a type I interferon (IFN-α and IFN-β) signature in dermatomyositis (DM) and JDM though the exact role interferon plays in disease is not well understood. More recently, the role of type II interferon (IFN-γ), a cytokine primarily secreted by T and NK cells that helps to link the innate and adaptive immune responses, has also been of interest in complex type I interferon–driven diseases.

In JDM, type II interferon–induced transcripts were found to co-localize with type I IFN–induced transcripts in muscle specimens, and the degree of both interferon scores correlated with T cell and monocyte infiltration as well as perifascicular atrophy [34]. Moreover, subjects with a higher type II interferon score at time of biopsy had more refractory disease with a longer duration to reach inactive disease. A type II IFN signature was also described using computational, data-driven meta-analytic methods of prior microarray datasets of DM and JDM muscle specimens and DM skin specimens, supporting a role of type II IFN in disease pathogenesis [35]. This analysis also found enrichment of class I MHC antigen processing, T cell activation, and enrichment of M1 inflammatory macrophages through cell enrichment analysis further supporting a role of IFN-γ. Parsing the contributions of type I and II IFN in an inflammatory environment is challenging because these molecules have several overlapping targets and will be an important focus of future research.

Adding to the complexity of what is known about interferon signaling in JDM, there is also new evidence that type I IFN signaling may exert beneficial angiogenic properties in certain cell types. Isolating endothelial and myogenic precursor cells from JDM muscle specimens, Gitiaux and colleagues used transcriptomics to show that both cell types are a source of interferon signaling [36]. However, the interferon signature in endothelial cells appears to promote an angiostatic signature that may promote the vasculopathy of the disease, whereas myogenic precursors secrete higher amounts of type I IFN in proportion to the degree of vasculopathy to promote angiogenesis. The authors highlight the complexity of interferon

signaling in this disease and remind us to consider the therapeutic implications of interferon blockade.

There are very few studies investigating expression signatures in JDM skin as skin biopsy is not as routinely performed as muscle biopsy for diagnostic purposes. Interestingly, a cross-tissue meta-analysis including muscle and skin specimens from DM subjects demonstrated striking similarity in gene expression between muscle and skin with enrichment of the same immune pathways, including type I and II IFN pathways, and cell types [35]. A type I IFN signature has been recapitulated in a recent study of 42 DM skin biopsies, and interferon scores correlated with the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity scores [36]. Studies to evaluate gene expression in JDM skin will be an important future direction given the differences in clinical phenotypes and disease course between juvenile and adult DM.

Immune Cell Phenotypes in JDM: Impaired Immune Regulation

Both innate and adaptive immune system activation occurs in JDM; however, the pathogenic cell types involved are not well understood. Exciting technological advances, including mass cytometry and single-cell sequencing, hold promise to help further elucidate cell types in the near future. Research to date and a clinical response to certain targeted therapies suggest that B cells, T cells, and innate immune cells, such as NK cells, play a role in JDM biology. Interestingly, many of these studies have suggested that impaired immune regulation may be at the heart of JDM biology.

A study applying mass cytometry to treatment-naïve JDM samples found that naïve B and CD4+ T cells were increased in JDM samples compared with those in controls and increased with treatment, whereas NK cells, believed to play an immune regulatory role, were decreased [37]. Using hierarchical clustering and feature selection, the authors identified PLCγ2 signaling in NK cells to be a feature distinguishing treatment-naïve JDM from healthy controls and further experiments suggested that dysregulated PLCγ2 signaling may lead to decreased NK cell cytotoxicity in JDM.

Because of the clinical response to rituximab in myositis [38] and the phenotypic importance of myositis-specific antibodies, many experts have been interested in the role of B cells. Sorting the B cell compartment by flow cytometry and then performing RNA sequencing, Piper et al. demonstrated expansion of immature transitional B cells in treatment-naïve JDM, which decreased with treatment, and expression of the type I interferon signature by these cells, suggesting these pro-inflammatory B cells may play a role in disease [39]. Furthermore, these B cells had impaired production of IL-10, a cytokine with immune regulatory effects, suggesting a skewing of this B cell population to a more inflammatory phenotype and immune dysregulation.

In addition to increased T cells in dermatomyositis histological muscle specimens, there may also be dysregulation of T cell effector mechanisms. Vercoulen et al. showed impairment of regulatory T cell (Treg) signaling in Treg cells isolated from the peripheral blood of JDM patients despite increased infiltration of these cells in the inflamed muscle [39]. Using an in vitro suppression assay, they found that Tregs isolated from a proportion of active JDM did not have the ability to suppress effector T cell function, whereas there was consistent suppression in patients with inactive JDM.

Biomarkers: Key to Developing a Personalized Treatment Strategy

Monitoring disease activity has always been challenging in JDM due to the lack of reliable biomarkers. Current assessments of disease activity are limited by the need for expertise of the physician, participation of the child, and inability to distinguish between activity and damage. Labs that are routinely drawn, including muscle enzymes and inflammatory markers, can be normal in some patients despite active disease. Physicians need tests that can stratify patient subgroups and accurately assess disease activity in order to titrate treatment. Promising studies measuring chemokines, cytokines, adipokine, and transcriptome signatures [40–42] suggest the reality of disease activity biomarkers in JDM is on the horizon. Furthermore, disease registries have helped characterize the myositis-specific antibody (MSA) profiles associated with JDM and the distinct clinical subtypes associated with these antibodies.

One of the most compelling stories thus far has been that of galectin-9 and CXCL10. In a study of 25 JDM patients measuring 45 proteins of interest, galectin-9 and CXCL10 were identified as potential biomarkers being significantly higher in JDM compared with healthy control subjects and also correlating with disease activity [43]. In a follow-up validation study including three independent cross-sectional and longitudinal JDM cohorts from an international study base, both galectin-9 and CXCL10 tightly correlated with disease activity and distinguished active from inactive disease with a higher sensitivity and specificity than the prototypical muscle enzyme, creatinine kinase (CK) [44]. In four JDM subjects with longitudinal data and flare, these biomarkers either remained high after initiation of treatment or steadily rose in the months before clinical symptoms of flare were evident, suggesting they might be predictive of flare. Moreover, early testing of these proteins on dried blood spots suggests these biomarkers could be used for at-home testing facilitating a precision medicine approach.

Because of the disease heterogeneity of JDM, great effort has been made to stratify patient subgroups. Remarkable work from the Childhood Myositis Heterogeneity Collaborative Study Group characterizing the clinical and demographic phenotypes

associated with MSAs has demonstrated that juvenile IIMs have profiles and phenotypes that are overlapping but distinct from adult IIM [5]. In juvenile myositis, p155/140 antibodies are the most prevalent MSA and associated with many skin manifestations, low CK levels, and a chronic illness course. This MSA was also found to be the most common MSA in a small cohort of JDM patients with clinically amyopathic disease [45]. The anti-MJ antibody is the second most common MSA in juvenile myositis and is characterized by more muscle involvement, calcinosis, hospitalization, and monocyclic disease course. Work out of a large European cohort identified anti-MDA5 antibodies to be present in 7.4% of JDM patients and associated with skin and oral ulcerations, arthritis, and interstitial lung disease in 4 of 21 patients [46]. The myositis-associated antibody, anti-Ro52, is present in about 14% of patients with juvenile myositis and has been found to be associated with both anti-MDA5 and antisynthetase antibodies, interstitial lung disease, and a more severe disease course [47]. While the pathogenicity of these antibodies remains unknown, this work highlights the utility of these antibodies in clinical practice to identify patients at high risk for certain disease manifestations, like lung disease, and to help prognosticate disease course.

Conclusions

Though we describe JDM as a single disease entity, the expressions of disease activity and severity vary affecting the skin, muscles, and virtually any organ system. In addition, patients do not respond uniformly to available treatments. There has been great progress in the standardization of the classification of disease in JDM as well as in the monitoring of disease to help us to better phenotype our JDM patients. These well-developed classification criteria as well as response criteria, in conjunction with improved and uniform data collection for JDM, will allow for improvement of our ability to monitor clinical and pathophysiologic disease heterogeneity and response to treatment. This work partnered with ongoing advances in science and technology will allow us to develop truly personalized treatment approaches and precision medicine approaches in the future which are expected to improve future morbidity and outcomes in JDM. These combined efforts and progress will allow for true personalized, precision medicine for our JDM patients in the future.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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