

CURE JM

UPDATE ON JUVENILE MYOSITIS CARE
AND RESEARCH
2019

**SUMMARY OF SCIENTIFIC
RESEARCH POSTERS**



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PARENT PERSPECTIVES ON ADDRESSING EMOTIONAL HEALTH FOR YOUTH WITH JUVENILE MYOSITIS: A QUALITATIVE FOCUS GROUP STUDY

Little is known about how Juvenile Myositis (JM) affects emotional health. We conducted focus groups with parents of youth with JM. Focus groups assessed how parents feel JM affects child/family emotional health and how to provide better support. Depression and anxiety were common, but so were strength and resilience, especially as children with JM grew older. Parents reported difficulty finding emotional support. Parents perceived that JM affects siblings and other family members emotionally and that their children with JM are often not forthcoming about their emotional needs. Parents desired counseling and peer support groups for their children.

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ABATACEPT IN JUVENILE DERMATOMYOSITIS (AID CLINICAL TRIAL)

Rodolfo Curiel, MD, Gulnara Mamyrova, MD, Olcay Jones, MD, and Lisa Rider, MD, at George Washington Myositis Center (GW MC) are conducting a research study of an experimental biologic therapy Abatacept, administered by subcutaneous injection, for refractory Juvenile Dermatomyositis (JDM) (clinicaltrials.gov identifier NCT02594735).

Pediatric and adult patients with JDM should have moderately active disease despite treatment with prednisone and at least one other medication. They must be at least seven years of age and weigh at least 66 lbs. to qualify for the study.

YOU MAY QUALIFY IF:

- You are an adult or child of at least seven years of age who has Juvenile Dermatomyositis (JDM).
- You have moderately active disease.
- You have had inadequate response or intolerance to prednisone and one other medication.
- You weigh at least 66 lbs.

STUDY DETAILS:

- Medical evaluations, study questionnaires, blood testing, and MRIs/x-rays will be performed at six visits over six months.
- No charge for study-related evaluations and testing.
- Travels funds and compensation available for study participants for five study visits after screening visit.
- If you are interested, please email study coordinator Hassan Awal at hawal@mfa.gwu.edu or call at (202) 741-2389.

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THE RELATIONSHIP OF PAIN, FATIGUE AND EMOTIONAL DISTRESS WITH QUALITY OF LIFE IN JUVENILE MYOSITIS

Juvenile Myositis (JM) can negatively impact quality of life (QoL) outcomes via muscle weakness and rashes. However, it is not well understood how pain, fatigue, and emotional distress might affect QoL in JM. In this study, we assessed the relationships of pain, fatigue and emotional distress to QoL in JM. We administered surveys to youth with JM and their parents, including PedsQL physical/psychological QoL forms and more recently developed PROMIS forms evaluating fatigue, pain, and emotional distress. We then tested whether fatigue, pain, depressive symptoms, or anxiety predicted physical and psychological QoL. Seventy-five patients/parents were enrolled in the study. We found a uniquely strong relationship between fatigue and physical QoL as measured by both patients and parents. Patient and parent perceptions differed with regards to the relationship of fatigue to psychological QoL; we recommend assessing both patient and parent viewpoints. Further study of fatigue and treatments for this symptom are needed in order to improve QoL.

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EARLY STAGE ASSAY AND DRUG DEVELOPMENT FOR MYOSITIS

The current immunosuppressive therapies for idiopathic inflammatory myopathies (myositis) are often not a cure and are accompanied by harsh side effects. We have recently initiated a program to find new or repurpose approved drugs for myositis. Early stage drug development involves identifying components of the body that can be modulated to treat a disease, creating test systems called assays to measure those components, and then testing large collections of chemical compounds with the assays to select potential therapeutics. Although the cause of myositis is not known, muscle from patients usually have too much of the inflammatory proteins interferon (IFN) and major histocompatibility complex class I (MHC class I), which are both thought to contribute to damage and weakness. We have developed a series of assays to identify chemical inhibitors of the IFN-stimulated expression of MHC class I in muscle, with the goal of reducing inflammation and autoimmunity in myositis. The primary high throughput screening assay that we created utilized CRISPR/Cas9 to genome-edit human muscle cells to attach an easily measurable enzyme at the end of MHC class I, so that we can quickly detect chemical compounds that decrease its abundance. We also developed several follow-up assays measuring gene and protein abundance to confirm the results. We are currently screening libraries and are presenting data here from a small, well characterized library of 1280 compounds that identified a handful of actives, which will be further evaluated. Chemical libraries containing new and approved drugs will be screened, and actives will need to be validated in cell culture, animal models, and clinical trials to ensure a safe and effective therapy for myositis patients.

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IMMUNE CELL EXPLOSIONS IN JUVENILE DERMATOMYOSITIS

Drs. Christian Lood, PhD, and Lauren Pachman, MD, are collaborating to discover how the most abundant circulating white blood cell, the neutrophil, contributes to the inflammatory processes in Juvenile Dermatomyositis (JDM). Neutrophils are important immune cells in our host defense and protect against invading bacteria. However, uncontrolled neutrophil activation is also linked to inflammation and disease, including autoimmunity. Dr. Lood recently found that neutrophils, when experiencing danger, may explode and cause local organ damage and inflammation in patients with SLE. In the current study we aimed to determine if children with JDM experience neutrophil explosions, whether neutrophils contribute to their disease progression, and if it is possible to intervene to limit the inflammatory process.

This collaborative work made several fundamental observations furthering our understanding on the role of our immune system in patients with JDM. Intriguingly, we found that neutrophils became frustrated, entering a premature cell death program leading to explosive release of inflammatory and harmful components into the tissue of children with JDM. We also identified remnants of the exploding neutrophil in their blood, which was associated with active severe disease, including calcinosis and dyslipidemia, an early stage of atherosclerosis. We were able to pinpoint several key factors involved in the explosive process and plan to develop novel therapies to interfere with this process. Finally, we anticipate that neutrophil biomarkers in the blood may be useful to monitor patients, and hopefully identify children prone to develop severe disease, including calcinosis and atherosclerosis, allowing for early intervention and prevention.

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MITOCHONDRIA – THE POWER PLANTS IN MUSCLE – ARE DAMAGED IN JUVENILE DERMATOMYOSITIS

Drs. Christian Lood, PhD, Stephen Doty, PhD and Lauren Pachman, MD, are collaborating to understand how damage to mitochondria contributes to JDM. Our body, and cells, require energy to function properly. Most of our energy comes from specialized power plants in each cell, called mitochondria. However, this energy production comes with a side effect – the generation of toxic material, reactive oxygen species (ROS). Dr. Lood recently described that in SLE patients, mitochondria experience a meltdown, causing cellular explosions, releasing harmful ROS and promoting inflammation. In the current study, we aim to investigate the status of the mitochondria in JDM patients, to document the type of damage sustained, and thus how they contribute to local inflammation and muscle weakness.

This collaborative work has made several novel observations. Using electron microscopy of untreated patients, we visualized the mitochondria in the JDM muscle tissue and found, to our surprise, that they were crystallized, unable to function properly and therefore not able to support the muscle with sufficient energy. Further, we acquired evidence of mitochondrial meltdown and cellular explosions, detecting remnants of the mitochondrial meltdown also in the blood of JDM patients, especially those JDM patients with calcinosis. These altered mitochondria were detected by the JDM immune system as “foreign” material, provoking the generation of mitochondria-specific autoantibodies in children with JDM. These autoantibodies were particularly elevated in children with calcinosis. Currently, we hope to devise methods to rescue the mitochondria from being either crystallized or disintegrated which may help to limit muscle damage and inflammation in children at the early stage of JDM. The first step is to develop a panel that can detect mitochondrial-related damage markers in the bloodstream. These biomarkers may assist in clinical care by identifying those children with JDM who are at risk for developing severe muscle weakness, facilitating early intervention and prevention.

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A CROSS-TISSUE GENE EXPRESSION META-ANALYSIS IN DERMATOMYOSITIS

Jessica Neely, MD, is interested in using studies of gene expression to better understand the immunology of Juvenile Dermatomyositis (JDM). Human DNA contains the instructions for nearly 20,000 genes, providing cells the information needed to make proteins. Gene expression is used to measure the levels of these instructions, called mRNA. Measuring mRNA can tell us what proteins cells are making and what genes are present. Prior studies of gene expression have helped us learn which parts of the immune system are involved, however, more can be gained by combining these studies into what is called a meta-analysis. By looking at gene expression in both muscle and skin tissues we can learn more about the similarities and differences in the biology of each tissue. These results can help us better understand the disease and find new treatments.

By combining all publicly available samples from muscle and skin in JDM and adult DM patients in a gene expression meta-analysis, Dr. Neely was able to identify several interesting gene expression patterns, or signatures, related to the immune system present in DM. She verified previous findings of a type I interferon signature and an MHC class I antigen processing signature. She also identified new signatures, including a type II interferon signature and T cell activation. These signatures were present in both muscle and skin tissues, highlighting that the gene expression is strikingly similar across different affected tissues in DM. Together, these findings, provide new insights into the immunology of JDM. With follow up experiments, Dr. Neely hopes to validate these findings and begin to explore how they could relate to new treatments.

Jessica Neely MD
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MYOSITIS AND AUTOIMMUNE DISEASE STUDIES AT THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)

Lisa G. Rider, MD, Adam Schiffenbauer, MD, and Frederick W. Miller, MD, PhD, are conducting several clinical research studies on myositis and autoimmune diseases in the National Institute of Environmental Health Sciences (NIEHS), one of twenty-seven institutes of the National Institutes of Health (NIH). Clinical research studies are exciting because the patient plays an active role in their health care and helps identify potential treatment options. Several studies at the NIEHS are underway and currently enrolling patients, including:

The Twin Sibling Study, which seeks to identify the genetic and environmental factors that may result in autoimmune disease in one sibling but not the other.

Researchers will look at individuals with juvenile or adult Myositis (diagnosed in the past five years), or other autoimmune conditions, and their close-in-age, same sex, healthy sibling or twin.

Lisa G. Rider, MD

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MYOSITIS AND AUTOIMMUNE DISEASE STUDIES AT THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS), CONT.

The MYORISK (Environmental Risk Factors for the Anti-Synthetase Syndrome) Study will explore whether certain factors are associated with Myositis, particularly in people with Jo1 or anti-synthetase autoantibodies, who typically have lung disease and/or arthritis.

The Myositis Natural History Study involves a comprehensive evaluation of each patient's Myositis and then NIEHS physicians can make treatment recommendations.

The Sodium Thiosulfate for Calcinosis Dermatomyositis Study will evaluate intravenous sodium thiosulfate as a treatment medication for calcinosis in adult or juvenile dermatomyositis patients.

These studies can significantly further research by establishing new knowledge, testing a possible new treatment, and getting closer to a cure.

Lisa G. Rider, MD¹
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TREATMENT TRIAL FOR CALCINOSIS IN JUVENILE AND ADULT DERMATOMYOSITIS

Adam Schiffenbauer, MD, and Lisa Rider, MD, are leading a treatment trial in the National Institute of Environmental Health Sciences (NIEHS), NIH, to test whether a drug called sodium thiosulfate is a good treatment for calcinosis in juvenile and adult DM patients.

The study will invite patients with juvenile and adult DM with moderate to severe calcinosis located on the arms, legs, trunk, or torso to the NIH Clinical Center for testing. The study is currently open to adult patients, but is expected to open soon to pediatric patients at least 7 years of age. If found to be eligible for participation, patients undergo pre-treatment tests to establish a baseline level of calcinosis and myositis disease activity. These assessments will include physical exams, blood and urine testing, imaging studies, visits with medical specialists like physical therapists, and at-home questionnaires. These assessments will occur throughout the entire study to make accurate measurements about disease activity and measure the effects of the sodium thiosulfate.

Once a pre-treatment period is complete, patients will start treatment at the NIH Clinical Center in Bethesda, Maryland, consisting of intravenous (IV) sodium thiosulfate (STS) treatment, three times weekly for ten weeks. Patients are monitored closely for any side effects during this treatment period.

After treatment has ended, follow-up calls between doctor and patient will update disease status. At 12 and 52 weeks after ending treatment, participants will return to the NIH for re-evaluation of their calcinosis and myositis disease activity. The entire study will last seventy-two weeks and reimbursement for participation is offered throughout the study. This clinical trial will help doctors and researchers better understand calcinosis and dermatomyositis in terms of detection, control, care and treatment.

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DEVELOPMENT OF BIOMARKER-BASED TREATMENT STRATEGIES IN JUVENILE DERMATOMYOSITIS

Annet van Royen-Kerkhof, MD, and Femke van Wijk, MD, are leading studies to improve the methods of identifying disease activity in Juvenile Dermatomyositis by specific proteins in the blood (biomarkers).

So far, there are few reliable clinical or laboratory markers that can predict what will happen in an individual patient. Therefore, all JDM patients are treated the same way, with high-dose immunosuppressive medication, which is continued until clinical improvements are evident and then reduced slowly over a two-year period (at least). However, some patients the medication might have been discontinued before the two-year period is completed. On the other hand, the risk of too early reduction of treatment is a flare of the disease that may be difficult to get under control and may cause further permanent damage to e.g. the muscles. Because clinical parameters are sometimes difficult to interpret, it would be very helpful to have objective laboratory markers that can monitor disease activity and predict the risk of a disease flare.

The group of van Wijk and van Royen in the Wilhelmina Children's Hospital of the University Medical Center in Utrecht, The Netherlands, has discovered two novel laboratory markers that can measure even low levels of disease activity in JDM. Recently these findings were validated in a large international collaboration study, and were performing better than the current laboratory markers like CK. The next step is the implementation of the markers into clinical practice. Therefore, a large group of JDM patients in different expert centers in the world will be followed-up, to determine whether 1) the identified biomarkers can indeed be used for flare prediction and disease prognosis and 2) a risk profile at onset of disease can be defined based on these and novel markers. With these findings we aim to introduce biomarker-guided treatment to prevent under and overtreatment of patients and improve their clinical outcome.

Annet van Royen-Kerkhof, Femke van Wijk
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ANTI-RO52 AUTOANTIBODIES IN JDM ASSOCIATE WITH INTERSTITIAL LUNG DISEASE AND INCREASED SEVERITY

Sara Sabbagh, DO, is interested in studying autoantibodies in Juvenile Dermatomyositis. Antibodies are a normal part of the immune system which help fight infection by recognizing a unique protein from the harmful agent, called an antigen. Autoantibodies are antibodies that are directed against an individual's own proteins. Patients with inflammatory myositis often have autoantibodies which are specific to their disease, called myositis specific autoantibodies. They can also have autoantibodies that occur in myositis in addition to other connective tissue diseases, called myositis associated autoantibodies. The role autoantibodies play in inflammatory myositis is largely unknown. However, patients with the same myositis specific autoantibodies often have shared features of their disease. Knowing which patients have what myositis autoantibodies can be useful to doctors, because identifying who is at risk for certain disease features can help doctors better manage and treat their patients.

Dr. Sabbagh's research in the Muscle Disease Unit in The National Institute of Arthritis, Musculoskeletal, and Skin Disease, National Institutes of Health, focused on assessing the prevalence and associated disease features in children with myositis that have a myositis associated autoantibody called anti-Ro52. Anti-Ro52 autoantibodies are known to occur in adult patients with myositis. They can be seen alongside myositis specific autoantibodies, but also have distinct features in adult patients with myositis. Using 302 juvenile myositis patient samples and comparing to juvenile healthy controls, Dr. Sabbagh tested for these autoantibodies in patients with juvenile dermatomyositis by enzyme-linked immunosorbent assay (ELISA), which is a technique that detects and quantifies antibodies.

ANTI-RO52 AUTOANTIBODIES IN JDM ASSOCIATE WITH INTERSTITIAL LUNG DISEASE AND INCREASED SEVERITY, CONT.

Her research has yielded interesting findings. Anti-Ro52 autoantibodies were found in 14% of juvenile myositis patients overall and found to occur in higher rates in juvenile myositis patients with lung disease. In addition, patients with anti-Ro52 autoantibodies were found to have more severe disease overall than myositis patients who were negative for anti-Ro52 autoantibodies. Knowing which patients are at risk for certain disease features based on their autoantibody status can help doctors manage their patients. Sometimes autoantibodies can determine what screening tests are appropriate for a patient. Other times, it can direct therapy choices. Overall, Dr. Sabbagh's data suggest that anti-Ro52 autoantibodies may impart clinical significance. This work was recently accepted for publication in *Annals of Rheumatic Disease*.

Sara Sabbagh DO1

1National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Bethesda, MD

GENETIC MARKERS OF TREATMENT RESPONSE TO RITUXIMAB IN JUVENILE DERMATOMYOSITIS

Cory Stingl, MD, is a pediatric rheumatology fellow and post-doctoral fellow in genomics at Duke University with a special interest in Juvenile Dermatomyositis (JDM). His research focuses on using markers in the blood to (1) understand why some children with JDM respond well to treatment, while others do not and (2) to predict whether a child will respond to specific treatments for JDM. This information may help doctors treating children with JDM start the most effective therapy at diagnosis, and thus minimize damage from the disease or adverse effects from treatments for disease flares.

Dr. Stingl's current work focuses on a medication called rituximab that is often used to treat JDM when children do not respond to standard first-line therapies. His research uses a specialized blood test called ribonucleic acid (RNA) sequencing, or RNA Seq. RNA Seq is a way for researchers to understand what biologic processes (called pathways) are active or inactive in the body. Analyzing these pathways and how they relate to treatment response with rituximab may help doctors better identify which children with JDM will respond to rituximab and which children will not. RNA Seq is underway for this project and we expect data analysis to begin in late spring.

Cory Stingl MD
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DEFINING MOLECULAR SIGNATURES OF SKIN DISEASE IN JDM.

CHARACTERIZING INFLAMMATORY CELL SUBPOPULATIONS AND CELLULAR ARCHITECTURE IN JDM SKIN

Juvenile Dermatomyositis (JDM) is a potentially life-threatening inflammatory myopathy of childhood characterized by muscle weakness, cutaneous disease and vascular dysfunction in multiple organ systems. In JDM, persistent skin disease predicts disease chronicity and is associated with premature cardiovascular disease. Whereas muscle inflammation improves with therapy, skin inflammation is challenging to treat and can lead to debilitating calcinosis and also vascular derangement. We need a better understanding of how skin disease can trigger widespread organ inflammation and improved biomarkers to determine the patients at highest risk of severe disease and poor response to therapy. The overall objective of this project is to characterize the genes, biological pathways and immune cells that are dysregulated in the skin of patients with JDM.

We first plan to obtain RNA from archived skin biopsy samples in JDM patients and analyze for changes in gene expression that might indicate disease activation pathways and new targets for therapy. In order to identify pathways uniquely activated in JDM, we will compare JDM molecular signatures to those in childhood-onset systemic lupus erythematosus (cSLE) and healthy controls. We will then use imaging mass cytometry to visualize the expression of multiple cell markers simultaneously within the environment of the whole tissue, which will allow us to identify variation in individual cell populations that may also be important for disease initiation.

We expect that defining the gene expression and cellular patterns of JDM will lead to improved disease classification systems and risk stratification of patients. This work will provide an essential foundation for future studies into potential disease mechanisms, biomarkers and therapeutic targets, leading to improvement in care for JDM patients.

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CLINICAL FACTORS ASSOCIATED WITH LONG-TERM DAMAGE AND CALCINOSIS IN AN ADULT-AGE REFERRAL POPULATION OF JUVENILE MYOSITIS PATIENTS

George Washington Myositis Center (GW MC) performs center-based research in myositis and collaborates projects within GWU, and with NIEHS/NIH and other myositis centers and translates new knowledge to clinical practice and improvement of myositis patients' health. Several research projects at GW MC are underway. One of recently completed research studies include "Clinical factors associated with long-term damage and calcinosis in an adult-age referral population of Juvenile Myositis patients". In this study, GW MC Team investigated long-term outcomes in patients with juvenile onset idiopathic inflammatory myopathies (JIIM) who are currently adults.

- Adults with JIIM were assessed at two referral centers between 1994 and 2016. Associations of multiple clinical, demographic, and laboratory factors with two long-term outcomes, a higher Myositis Damage Index (MDI) and the presence of calcinosis on last evaluation, were examined.
- 49 patients with JIIM (37 dermatomyositis, 5 polymyositis, 7 overlapping myositis) had a median age of 24 years and median follow-up period of 12 years after diagnosis. 63% of patients had a chronic, 31% a polycyclic, and 6% a monocyclic illness course.
- Disease Damage was present in 96% of patients with median MDI score of 6 (range 1-10).

CLINICAL FACTORS ASSOCIATED WITH LONG-TERM DAMAGE AND CALCINOSIS IN AN ADULT-AGE REFERRAL POPULATION OF JUVENILE MYOSITIS PATIENTS, CONT.

- Cutaneous (in 80% of patients) and muscle (in 78% of patients) damage were most frequent and most severe. Calcinosis was present in 55% of patients.
- Erythroderma, shawl sign, disease duration, worst functional class, and heliotrope rash were independently associated with higher MDI.
- Disease duration, younger age at diagnosis, falling episodes, Gottron's papules, clinical subgroup JDM, constipation, periungual capillary changes, lipodystrophy, and contractures were strongly associated with calcinosis.

This is one of the largest cohorts of patients with JIM evaluated for long-term outcomes into adulthood. Multiple clinical factors associated with long-term damage and calcinosis when JIM patients become of adult age, which included specific cutaneous and musculoskeletal features.

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MITOCHONDRIAL DNA: A NOVEL DRIVER OF TISSUE DAMAGE IN THE RARE DISEASE JUVENILE DERMATOMYOSITIS

Meredyth Wilkinson, PhD, from The University College of London is interested in finding new angles to treat Juvenile Dermatomyositis (JDM). The main treatments for JDM are steroids and strong immunosuppressive drugs. These treatments do not work for all patients and can cause side-effects. If we could understand which part of the immune system was going wrong it would help the development of more effective drugs. Dr. Wilkinson recently analyzed genes and how they are being expressed in JDM patient immune cells from the blood. Genes that code for mitochondria (the 'powerhouse' energy producers of the cell) were less active while genes that code for interferon (anti-viral response) were more active in JDM patients. This gene expression was evident on those patients on powerful treatments when compared to healthy children of the same age. These sets of genes offer the potential for new targets for treatments for JDM.

Dr. Wilkinson is investigating how problems with the mitochondria might cause inflammation in JDM. Mitochondrial problems can lead to the release of mitochondrial DNA (mtDNA) into the blood. mtDNA is similar to DNA in bacteria, so when mtDNA is in the blood it might be recognized as bacteria-like by the body's immune system, and initiate inflammation. Dr. Wilkinson is measuring mtDNA levels in JDM and healthy control samples to determine if there is a link between mtDNA levels and markers of disease activity. To determine if mtDNA can trigger inflammation, Dr. Wilkinson is creating a disease model in the laboratory, maintaining human immune and muscle cells in culture (simulation of the human body), and incubating them with isolated mtDNA. The measurement of specific inflammatory markers are then being used to establish whether mtDNA causes inflammation. To investigate the exact pathways that cause this effect, Dr. Wilkinson is introducing known drugs that can improve mitochondria function and prevent the release of mtDNA.

If mtDNA-triggered inflammation affects JDM patients, then drugs that target this pathway, such as antioxidants, could form the basis of new treatments. Furthermore, patients could be stratified by amount of mtDNA in the blood. This would facilitate new targeted treatments that could lead to use of less steroids, reduced drug side-effects and earlier time to disappearance of disease signs and symptoms.

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**OUR SINCERE THANKS TO THE
RESEARCHERS**

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SUMMARY OF SCIENTIFIC RESEARCH POSTERS

