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Kre-Celazine® as a Viable Treatment for Juvenile Rheumatoid Arthritis/Juvenile Idiopathic Arthritis — A Pilot Study

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ABSTRACT The purpose of this study was to ascertain whether an oral, non-prescription, nutritional supplement compound composed of a proprietary alkali-buffered creatine monohydrate and cetylated fatty acids mixture (Kre-Celazine®) was efficacious in reducing or eliminating refractory pain and inflammation, without untoward effects, in Juvenile Rheumatoid Arthritis (JRA), which is also called Juvenile Idiopathic Arthritis (JIA). JRA/JIA is a patho-physiologically complex, chronic childhood autoimmune inflammatory disease of unknown etiology. Numerous studies have unsuccessfully attempted to pinpoint a possible common initiation event. Officially considered an affliction of children below the age of 16 years, an initial diagnosis has been confirmed in infants less than 1 year old, to individuals older then 17 years. In this study, sixteen juveniles, ages 7 through 16 years, experiencing long-standing, unremitting pain and inflammation despite previous use of prescription anti-inflammatory drugs and NSAIDs, were enrolled in a 30-day, open-label clinical study and treated with Kre-Celazine. Efficacy of this nutritional supplement was determined by the juvenile's personal physician and based on observations of the following: (1) significant reduction or elimination of palpable signs of inflammation; (2) renormalization of range of motion; (3) reduction or absence of perceived pain as reported to the physician by the patient; (4) renormalization of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values. In addition, the individual's previous steroid or non-steroidal anti-inflamatory medication(s) were reduced or eliminated in a stepwise progressive fashion during the study.

KEY WORDS: • ***autoimmune*** • ***juvenile rheumatoid arthritis/juvenile idiopathic arthritis (JRA/JIA)*** • ***Kre-Celazine*** • ***nutritional supplement*** • ***pauciarticular*** • ***polyarticula*** • ***systemic onset***

INTRODUCTION

Juvenile rheumatoid arthritis/juvenile idiopathic arthritis (JRA/JIA)[1,2] is a patho-physiologically complex chronic childhood autoimmune-related inflammatory disease of unknown etiology. As of 2009–2010, the most common form of juvenile arthritis was considered to be JRA. The CDC website states that this affliction is classified as ''affecting children below the age of 16 years.'' However, an initial diagnosis of JRA has been confirmed throughout the entire age spectrum, from infants younger than 1 year old to individuals older then 17 years.

Numerous studies have attempted to pinpoint a possible common initiation event for this condition (*e.g.*, exposure to various pets, insect bites, soil exposure, specific bacterial or viral infections, emotional stress, specific gene activation, hormonal involvement, a preceding illness such as rheumatic fever, etc.) yet no single—or multiple—contact or infectious JRA triggers have ever been confirmed. Because this type of autoimmunity frequently impacts one or multiple organs in the body, JRA/JIA is sometimes referred to as a systemic illness or rheumatoid disease.[3–6] Unlike adult rheumatoid arthritis (ARA), inflammation tends to present more often in larger joints, such as knees, wrists, and ankles (as opposed to fingers, which is characteristically observed in ARA). Also, unlike ARA, in which women are more often afflicted then men, only two of the three sub-classifications (pauciarticular and polyarticular) have shown a clear female gender preference.

Depending upon its symptomatic manifestations within the first 6 months of onset, JRA/JIA is classified as pauciarticular (adversely affecting 4 or fewer, predominantly larger joints), polyarticular (impacting at least 5 joints, primarily large, as well as a few small joints), and systemic onset (aggressively active, fibril, and painfully inflammatory, small and large joints, as well as multi-organ involvement). Polyarticular and pauciarticular account for over 40% and 50% of the JRA/JIA cases, respectively.[7]

The issues that must be addressed regarding onset of arthritic inflammation in individuals fall into two categories: the slower, chronic, milder inflammation type in which symptoms

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tend to respond more favorably to older anti-inflammatory treatments (NSAIDs, Methotrexate, etanercept,);[8,9] and systemic onset, the rarest form of the disease, accounting for between 10% and 20% (average 15%) of cases, and displays no gender preference. Persons in this category suffer spiking fevers, severe joint and soft tissue inflammatory symptoms, accelerated joint erosion, and organ complications. Systemic onset is extremely challenging to treat.[10] Common blood test hallmarks of this disease subtype are grossly elevated levels of anti-nuclear antibodies (ANA) and blood inflammatory markers, such as C-reactive protein (CRP) and abnormal erythrocyte sedimentation rate (ESR) which, by themselves, are not indicative of any specific illness. Systemic onset is, therefore, diagnosed primarily by febrile onset and its other characteristically aggressive physical symptoms.

In this pilot study, the aim is to evaluate the safety and efficacy of a nutritional supplement (Kre-Celazine®) in the setting of inflammatory JRA/JIA. This proprietary blend of cetylated fatty acids and an alkaline-buffered creatine monohydrate had demonstrated anti-inflammatory properties in earlier adult human test subjects. Its components have been reported to have potential anti-inflammatory properties and activity.[11,12] Fatty acids have the ability to reduce inflammation, though the precise mechanism through which this occurs in humans has not yet been confirmed. This anti-inflammatory characteristic, especially for the n-6 fatty acid group, may down-regulate or disrupt the inflammatory process through one or more mechanisms: (1) by removal of the proinflammatory factor, leukotriene B, from previously stimulated neutrophils and/or interleukin-1 monocytes; (2) by direct suppression of leukocyte activity; or (3) interfering with the adhesion molecule's expression through direct interaction with the cell membrane.[13,14] The anti-inflammatory action of cetylated monounsaturated fatty acids[15] is believed to arise from the inhibition of the cyclooxygenase pathway, though this has yet to be confirmed in human subjects. If the mechanism is finally elucidated in humans, this would be an important step in understanding not only general inflammation, but also the development of atherosclerosis as well as tumor progression.[16] It has been observed that cyclooxygenase-derived prostaglandin E2 is a known proinflammatory lipid mediator. This mediator has also been shown to be capable of promoting the progression of tumors in humans.

Creatine supplementation has been shown to influence endothelial permeability and cell surface reactivity. Nomura demonstrated that, in cell culture, creatine supplementation clearly showed anti-inflammatory activity by potentially interfering or blocking an inflammatory stimulus.[17] *In vitro* endothelial cell adhesion experiments demonstrated that, as creatine concentrations increased, the suppression of neutrophil adhesion to endothelial cells and endothelial permeability induced by serotonin and water decreased. Creatine supplementation also inhibited the expressions of inter-cellular adhesion molecule 1 (ICAM-1). In addition, E-selectin on the endothelial cells membrane occurred. By changing membrane permeability, or the way in which cell and molecular antagonists interact with the membrane's surface, creatine and/or its phosphorlated form, could directly exert a potential anti-inflammatory effect.[17] Whether or not the anti-inflammatory mechanism involves a function of receptor gating or competition, remains to be elucidated.

In this clinical trial we recruited children previously diagnosed with JRA/JIA who either did not tolerate or had an inadequate response to standard therapy (steroids and NSAID). The efficacy of Kre-Celazine was determined by the juvenile's treating physician and the participant, and was based on the following criteria: significant reduction or elimination of palpable swelling-related inflammation ($>30\%$); renormalization of range of motion; reduction or absence of perceived pain by the participant during daily activity and during physician initiated palpation; renormalization of CRP and ESR values.

MATERIALS AND METHODS

Participants

Juveniles less than 17 years of age who were suspected of having arthritis were referred to the treating hospital for the JRA/JIA, the Specialized Hospital for Active Treatment of Childhood Diseases Ltd. (SHATCD Plc) in Sofia, Bulgaria. Potential candidates were selected from juveniles who had met the following admission criteria for this study: less than 17 years of age; confirmed JRA/JIA; unresponsive to standard anti-inflammatory therapy (*e.g.*, Diclofenac Duo, Voltaren, Medrol, Sulfasalazine, Piascledin, Hydroxychloroquine, Artrochin, Methotrexate, Embrel); and a clear demonstration of palpable signs of inflammation, restricted range of motion as determined by their physician, elevated inflammatory markers, CRP and ANA, as well as accelerated ESR. Informed consent was sought from the parent(s) or guardian and was obtained before each juvenile was admitted to an open-label study. Each juvenile acted as their own control, in accordance with the policies and procedures of the ethics committee of the SHATCD Plc, in compliance with the Helsinki Declaration. The average age of all participants was 13.3 years. The age of first diagnosis ranged from age 2–3 years (31%) to age 15–16 years (12.5%). All juveniles had at least one afflicted joint and inflamed surrounding tissue.

Inclusion criteria

The following Inclusion Criteria was used:

1. Juvenile less than 17 years of age.
2. Previous diagnosis of JRA/JIA (pauciarticular, polyarticular, or systemic onset).
3. Unresponsive to standard anti-inflammatory therapy.
4. Palpable signs of inflammation.
5. Restricted range of motion.
6. Elevated inflammatory markers (CRP, ANA, ESR).
7. Non-diabetic.
8. Does not smoke.
9. Does not drink alcohol.
10. Does not have digestion problems.
11. Has no known organ failure (*e.g.*, kidney, heart, liver).
12. Does not currently take a nutritional supplement for pain.

Table 1. Pain Scores and Blood Laboratory Values, Pre- and Post-Treatment, for ANA, CRP, and ESR

Participant	*Initial pain scores by the patients*[a]	*Final pain scores by the patients*[a]	*Initial labs — Reference value ANA – 1:40 or less CRP – mg/L (less than or equal to 6 mg/L) ESR – mm/hr (less than or equal to 20 mg/L)*	*Final labs*
1 DT-m	3	0 and 1	ANA – 1:640 CRP – 9 mg/L ESR – 22 mm/hr	 CRP – 5 mg/L ESR – 5 mm
2 DM-m	3 and 4	0 and 0	ANA – 1:640 CRP – 8 mg/L ESR – 18 mm/hr	 CRP – 4 mg/L ESR – 6 mm
3 DD-m	3 and 4	0 and 0	ANA – 1:320 CRP – 5 mg/L ESR – 19 mm/hr	 CRP – 4 mg/L ESR – 10 mm
4 ET-m	3 and 5	0 and 1	ANA – 1:1,280 CRP – 18 mg/L ESR – 32 mm/hr	 CRP – 6 mg/L ESR – 20 mm
5 PV-f	4	1	ANA – 1:1,280 CRP – 11 mg/L ESR – 28 mm/hr	 CRP – 6 mg/L ESR – 16 mm
6 AB-m	2	1	ANA – not reported CRP – 7.04 mg/L ESR – 3 mm/hr	 CRP – 2.18 mg/L ESR – 3 mm/hr
7 BI-f	2	0	ANA – not reported CRP – normal ESR – 6 mm/hr	 CRP – normal ESR – 7 mm/hr
8 NS-f	2	0	ANA – normal CRP – normal ESR – normal	 CRP – normal ESR – normal
9 PV-m	2	1	ANA – normal CRP – normal ESR – normal	 CRP – normal ESR – normal
10 TS-f	2 and 1	1 and 0	ANA – normal CRP – 26.4 mg/L ESR – 39 mm/hr	 CRP – 20 mg/L ESR – 19 mm/hr
11 GA-f	3	0	ANA – 1:160 CRP – normal ESR – normal	 CRP – normal ESR – normal
12 ST-m	4 and 5	0 and 1	ANA – normal CRP – 103 mg/L ESR – 50 mm/hr	 CRP – normal ESR – 25 mm/hr
13 TK-m	3	2	ANA – normal CRP – 30 mg/L ESR – 12.2 mm/hr	 CRP – normal ESR – 12 mm/hr
14 VS-f	3	0	ANA – 1:160 CRP – normal ESR – normal	 CRP – normal ESR – normal
15-YP-f	3	2	ANA – 1:160 CRP – normal ESR – normal	 CRP – normal ESR – normal
16-EN-m	2 and 3	2 and 1	ANA – normal CRP – 99.77 mg/L ESR – 40 mm/hr	 CRP – 16 mg/L ESR – 20 mm/hr

[a]Pain score scale, 0 = no pain to 10 = worst pain imaginable.

ANA, anti-nuclear antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Exclusion criteria

The following Exclusion Criteria was used:

1. Is pregnant or breast feeding.
2. Has a fat malabsorption-related disease.
3. Is taking a lipid-absorbing or blocking agent (cholestyramine, ezetimibe).
4. Has chronic liver (hepatic) disease such as hepatitis or cirrhosis.
5. Has cancer (any form).
6. Has a medical condition that would preclude participation in this study.

Treatment

A specific control, or placebo, group was not designated for this open trial because each individual had already proven unresponsive to a spectrum of commonly prescribed drugs for this condition. A child or juvenile was considered unresponsive if, after a period of weeks, the treating physician determined that there was no significant reduction in inflammatory markers, palpable painful areas, and visible swelling.

Each participant received two 750 mg capsules (total 1,500 mg) of Kre-Celazine, an oral, non-prescription, nutritional supplement composed of a proprietary alkali-buffered creatine monohydrate and cetylated fatty acids mixture. This dose was to be taken daily (once in the morning and once in the evening, on an empty stomach, with water only) for a period of 30 consecutive days. Each family was provided with a Pain Journal to be completed weekly, in which they could indicate the perceived level of physical discomfort for each afflicted joint with a pain scoring system (0 = no pain to 10 = worst pain imaginable). At the conclusion of the 30-day treatment period, each individual returned to the hospital for re-examination and a fasting blood draw.

Biochemical analysis

Blood laboratory analyses of ANA, CRP, and ESR were performed at the start of the study. Individually, these tests are not directly indicative of any one condition. However, taken together, they are reasonably reliable markers of arthritic inflammation.

The normal reference values for these tests drawn at this laboratory are as follows:

ANA – 1:40 or less
CRP – mg/L (less than or equal to 6 mg/L)
ESR – mm/hr (less than or equal to 20 mg/L)

Physical analysis

Physicians palpated the same areas of inflammation both at the beginning and the conclusion of the study and their findings were subjective: no pain, light pain, or significant pain. By the end of the study, none of the juveniles had a pain score higher than light pain.

RESULTS

As depicted in Table 1, each of the 16 participants began with at least one joint/tissue event that they considered painfully significant (+2 or greater on the pain score scale of 0–10), and a range-of-motion restriction that was determined by their physician and reported subjectively as either not restricted, restricted, or significantly restricted. Weekly entries in the participant's journal indicated a stepwise reduction in perceived pain. By the end of week four, 13 out of 16 participants (81%) reported in their home Pain Journals, pain scores of 0 or 1. With the exception of a single participant, previously abnormal CRP labs renormalized, and ESR values (where listed) were universally reduced. The ANA tests performed at the beginning of the study were not repeated at the end of the 30-day period because ANA is not commonly tested at intervals shorter than three months. Attending physicians reported that almost all visible or palpable inflammation had disappeared in all but three individuals. Range of motion was rated as ''normal'' in all individuals by the participant's attending physician according to their individual criteria. Two of the participants reported feeling fully recovered and began playing basketball at school. None of the participants reported any incidents of stomach upset with the use of this product. There were no untoward events reported by the medical personal.

DISCUSSION

JRA/JIA individuals have multifaceted and complex medical needs. While the standard anti-inflammatory regime is usually effective in managing flare-ups in most individuals, a small sub-population continue to have muscle and joint pain, restricted range of motion, and require increasingly aggressive treatment resulting in undesirable side effects.

Treatment with Kre-Celazine led to a significant improvement and, in some cases, resolution of symptoms in juveniles who had not obtained satisfactory relief from their previous prescription medication. Based on the experiences reported in this study, as well as those of a previous study using arthritic adults, individuals with arthritic inflammation of the knee, ankle, foot, shoulder, elbow, wrist and hand will all benefit from the use of this nutritional supplement.

ACKNOWLEDGMENTS

The project received approval from the Ethics Commission of the Specialized Hospital for Active Treatment of Childhood Diseases Ltd. (SHATCD Plc) on June 13, 2011. The study was assigned the IRB No: 44.

AUTHOR DISCLOSURE STATEMENT

Jeff Golini is the CEO and Executive Scientist of All American Pharmaceutical. He is the developer of the proprietary compound, Kre-Celazine. Wendy Lou Jones, of Royal Knight Incorporated, has been retained as a

scientific consultant and for the technical writing services. She is the architect of this study.

The Specialized Hospital for the Active Treatment of Childhood Diseases Ltd. (SHATCD Plc) at the Boulevard Academy, in Sofia, Bulgaria, worked on a fee-for-service basis during this study.

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