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ORIGINAL ARTICLE

Post Chikungunya Arthritis: A Real Diagnostic and Therapeutic Challenge

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ABSTRACT

Objective: To evaluate the response of disease modifying anti rheumatic drugs (DMARDs) on patients diagnosed with post chikungunya inflammatory arthritis attending outpatient department of Rheumatology, Jinnah Medical College Hospital, Karachi, Pakistan.
Methods: This prospective case series study was conducted at Rheumatology clinic of Jinnah Medical College Hospital in Karachi, Pakistan from January – June 2017 after a serious Chikungunya outbreak in November 2016. All patients diagnosed with Chikungunya viral fever who had joint pain refractory to non-steroidal anti-inflammatory drugs (NSAIDs) were evaluated. All eligible patients were given a trial of DMARDs along with systemic steroids (tapering) for 6 months. Clinical response and inflammatory burden were evaluated using the Disease Activity Score (DAS 28).
Results: Of 112 patients, more than half the population, 65/112 (58%) was in acute flare of disease at the beginning of study and interestingly not a single patient had high disease activity (DAS >5.1) at the end of 6 months. Patients who went into disease remission were able to lead a pain free life, while those with a relatively higher DAS28 were still struggling with the disease. The overall response to the therapy was eloquent. None of the patient remained in active flair by the end of 6 months. The mean DAS significantly decline at 6 months as compared to the baseline DAS (2.79 ±0.89 vs. 4.96 ±1.11 respectively, p-value <0.001)
Conclusion: Chikungunya virus can lead to symmetrical inflammatory arthritis that phenotypically mimics Rheumatoid arthritis but is not primarily Rheumatoid arthritis. The pathogenesis of the disease process is still under study. It is concluded that there is a significant role of DMARDs in treating arthritis associated with CHIKV which can be used in controlling the inflammation and disease progression.
Keywords: Chikungunya (CHIK), Arthritis, Disease modifying anti rheumatic drugs (DMARDs), Non-steroidal Anti-inflammatory drugs (NSAIDs), Disease activity score 28 (DAS 28)

INTRODUCTION

Chikungunya virus is an arbovirus belonging to family, Togaviridae and genus Alphavirus is transmitted to humans by infected Aedes mosquitoes. After mosquito bite, the virus enters the skin and blood stream. Initial replication takes place in dermal fibroblasts after which the virus spreads through the blood to different organs including liver, spleen, lymph nodes, brain, muscle and joints. The viremic period in vertebrate host may last 2 to 10 days after acquiring the infection. The virus was first described during a febrile illness outbreak in Makonde in 1952, a province of Tanzania. The word Chikungunya is derived from the Bantu Language which means "that which bends up" and this refers to the position adopted by patients due to severe joint pain.[1]

Various risk factors that contribute to the spread of Chikungunya have been identified including rise in urbanization, weak healthcare framework in developing countries and a change in climate with augmentation of mosquito vectors.[2] Chikungunya fever was initially misdiagnosed as dengue before the twentieth century. The virus reached Western hemisphere with an outbreak on Island of Saint Martin in 2013.[3]

Since a re-emergence of this virus in year 2004, it has spread into new locations such as Europe and has led to countless cases throughout countries and around the Indian Ocean.[4] Karachi, a city in Pakistan, suffered a similar massive outbreak in November 2016 in which more than 30,000 people were affected by the virus. Clinically, it initially presents with sudden onset fever, polyarthralgia, rash, headache, nausea, fatigue and myalgia. The disease itself is self-limiting, joint pain can be persistent for months and even years in some cases.[5]

At present there are no vaccines or anti-viral drugs for the prevention and treatment of CHIK viral infection. However, multiple drugs are under trial. Treatment remains symptomatic with analgesics, anti-pyretic and NSAIDs.[6]

METHODS

This prospective case series study was carried out at the Rheumatology clinic of Jinnah Medical College Hospital in Karachi, Pakistan, over a period of 6 months, from January – June 2017 after a serious Chikungunya outbreak in November 2016.

The inclusion was all adult patients aged more than 18 years of either gender having positive sign and symptoms of polyarthritis, synovitis, ESR>30 and normal levels of serum Beta HCG in females of child bearing age, excluding underlying pregnancy. Whereas patients having oligoarthritis, prior history of Rheumatoid arthritis, positive RA factor, positive anti CCP and females with elevated levels of serum Beta HCG were excluded from the study. Upon ultrasonography 2 females with elevated levels of serum Beta HCG were found to be 5 weeks and 7 weeks pregnant, respectively. ESR, CRP, RA factor and Anti CCP levels were determined of all patients, using standard assays.

Disease burden was calculated using the disease activity score (DAS) 28 score and patients were classified accordingly. (Table 1)

Table 1: Categories of disease activity score (DAS)

Score	Disease Activity Score
<2.6	Remission
2.6-3.19	Low Disease Activity
3.2-5.1	Moderate Disease Activity
>5.1	High Disease Activity

All patients were evaluated for their joint pain which persisted after chikungunya infection, refractory to NSAIDs. Diagnostic evidence of infection, for all patients, was obtained already either by PCR technique during the acute stage or by the presence of anti CHIK antibody (IgM/IgG) as detected by ELISA> Out of these 264 patients, 112 were included in the study who fulfilled the inclusion criteria.

These selected patients were now diagnosed as having "*Post chikungunya inflammatory arthritis*" and were treated with synthetic DMARDs, Leflunomide (20mg/day) and Hydroxychloroquine (200mg twice daily) along with systemic steroids (10mg/day) which were tapered and stopped at 6 weeks. The steroids were given to relieve the acute pain until the slow acting DMARDs come into action. Female patients of childbearing age were asked to abstain from pregnancy for at least the next 6 months and practice safe contraception.

All patients were followed over a period of 24 weeks (6 months) and were monitored through DAS 28 score, calculated at Day 1 (beginning of treatment), 3rd month and 6th month respectively.

IBM SPSS Statistics for Windows, version 21 was used for data analysis. Descriptive statistics were explored using mean ±SD for quantitative variables like age and DMARDs whereas frequency and percentages for qualitative variables like gender and DAS score. Paired t-test was applied to see the mean difference of DAS score at day 1 and 6 months of the treatment. p-value <0.05 was considered as significant.

RESULTS

A total of 112 patients were included. Out of these 71 (63.3%) were females and 41 (36.5%) were males with moderate disease activity (mean ± SD DAS 4.96 ± 1.11). Amongst female population, 46 (64.8) were of childbearing age with serum Beta HCG within normal limits.

The DAS 28 on initiation of the therapy revealed more than half the population, 65 (58%) to be in acute flare of the disease (DAS >5.1). No patient was in remission (DAS<2.6), 15 (13.4%) had low disease activity (DAS 2.6-3.19) while 32 (28.6%) had moderate disease activity (DAS 3.2-5.1). On 3rd month, 19 (17%) patients went into remission and the number of patients having flare of the disease dropped down significantly to 18 (16%). At this point 27 patients (24%) had low DAS and 48 (42.3%) had moderate DAS. (Table 2) DAS score at the end of 6th month revealed a significant (p-vale < 0.001) response with none of the patient having high grade disease and the highest number of patients, 43 (38.4%), were seen in remission. The number of patients left with low and moderate disease were 41 (36.6%) and 28 (25%) respectively. Overall, patients were left with low disease activity (mean ± SD DAS 2.79 ± 0.89) at the end of our study. (Table 3)

Although the therapy was not discontinued after 6 months, we concluded our study as the duration of therapy is still not decided.

DISCUSSION

The present study was conducted during CHIK viral outbreak in Karachi, Pakistan. Patients included in this study were those who presented with polyarticular inflammatory joint pain. Multiple studies worldwide have shown that CHIK virus leaves a long lasting burden, typically involving the musculoskeletal system. A 6 year retrospective case series conducted in Reunion

Table 2: Outcome of DMARDs on DAS 28 score at different time intervals

DAY 1	n	%
Remission	0	0
Low DAS	15	13.4
Moderate DAS	32	28.6
High DAS	65	58
3rd MONTH		
Remission	19	17
Low DAS	27	24.1
Moderate DAS	48	42.3
High DAS	18	16
6th MONTH		
Remission	43	38.4
Low DAS	41	36.6
Moderate DAS	28	25
High DAS	0	0

DAS 28 categories: Remission <2.6, low DAS 2.6-3.19, Moderate DAS 3.2-5.1, High DAS >5.1
DMARDs: Disease Modifying Anti Rheumatic Drugs, n: number

Table 3: Mean difference of disease activity score at baseline and at six months

Disease Activity Score	Mean ±Standard deviation	P-Value [a]
Baseline	4.96 ±1.11	<0.001[b]
At six months	2.79 ±0.89	

a. Paired t test applied
b. Significant

Island showed 94 out of 159 patients, who were previously free from any articular disorder, acquired rheumatological diseases including Rheumatoid arthritis, spondyloarthropathies and undifferentiated polyarthritis.[7]

A similar finding like current study was reported from Saint Martin where an old age woman acquired severe joint pain after CHIK viral fever, affecting multiple joints (more than 10), not responding to NSAIDs and steroids. She was later diagnosed with seronegative, nondestructive, post chikungunya rheumatoid arthritis, treated with synthetic DMARD Methotrexate.[8]

Two phases of the illness have been recognized: acute viremic phase followed by chronic arthritis. Management of acute period remains symptomatic while that of the latter phase is determined by understanding the underlying disease process; whether the chronic arthritis is secondary to the persistence of viral infection or due to a post infectious inflammatory process.[9] Interleukin-17 in particular is responsible for chronic joint pain and stiffness, stimulating the upregulation of other inflammatory cytokines like Interleukin-1, Interleukin-6 and TNF α.[10] Patients who fulfilled the inclusion criteria of our study were those suffering from chronic phase of the illness.

In the chronic stage of the disease, arthritis can be present for weeks, months or even years. It has a significant impact on the quality of life of a patient with restriction of normal activities of daily life.[11-13] Majority of our patients attained remission by the end of 24 weeks but a certain number population still had persistent joint pain because of which they had to struggle with their daily chores.

A study carried out in George Washington University found patients, infected with CHIK virus, to have joint pain that can persist too as long as 20 months post infection.[14]

Detection of CHIK virus in blood can be done either by serology (IgM/IgG) or by PCR.[15] Polymerase chain reaction (PCR) is a reliable test to detect the presence of virus only in first seven days, after which it becomes undetectable. Five to ten days post infection, IgM Antibody to the virus becomes detectable and remains positive to a maximum of 2 to 3 months duration. Antibody IgG, like any other infection, shows chronicity of the disease and remains positive for years.[16]

Therefore, as a general rule serology should not be checked in the first week of illness.

We presumed the post infectious arthritis, in our population, to be autoimmune in origin. Based on this phenomenon we had decided to treat our patients with DMARDs. Further evidence to this can be drawn from a cross sectional study, which is one of the largest observational study that involved analysis of synovial fluid of chikungunya arthritis patients. Fluid analysis did not detect the presence of the virus. On the basis of these results, Dr. Chang explained the arthritis being secondary to the induction of host autoimmunity which justifies the role of immunomodulating drugs in its treatment.[17] Hydroxychloroquine (HCQ) has been recommended by Brito and colleagues as first line treatment for chronic chikungunya arthritis in a dose of 6mg/kg. However, they also suggested escalating the therapy to a combination of Hydroxychloroquine (HCQ), Sulfasalazine (SSZ), and Methotrexate (MTX) in patients with refractory arthritis.[18] The same triple therapy, as mentioned above, was found to be superior to HCQ monotherapy in an open labelled trial where patients were given MTX (15mg/week), SSZ (1000mg/day) and HCQ (400mg/day).[19] Although combination therapy was more effective, contribution of SSZ separate from MTX could not be established. The Brazillian Society of Rheumatology also recommends use of HCQ for the treatment of chronic joint symptoms following chikungunya fever. It may be used alone or in combination with other DMARDs.[20] Treatment of chronic Chikungunya arthritis in the above mentioned studies include Methotrexate with Sulfasalazine combined with Hydroxychloroquine. However, we combined Hydroxychloroquine (44mg/d) with Leflunomide (20mg/d), which is an established drug in treatment of Rheumatoid arthritis and we found this combination to be more efficacious when compared to the aforementioned trials, as shown in the results.

The choice of DMARDs to treat Chikungunya arthritis can vary, Mohini. A Gani in her study proves the efficacy of Methotrexate, Hydroxychloroquine and Sulfasalazine in treating post Chikungunya inflammatory arthritis. These drugs were continued for 2 years. Majority of patients in this study were positive for Anti-CCP.[21] We did not include in our study patients who tested positive either for RA factor or Anti-CCP in order to avoid the study from being biased. It is now important to consider the diagnosis of Chikungunya in travelers, presenting with symmetrical polyarthritis, returning from endemic areas.

This study has certain limitation. Firstly, this study is a single center study with a limited patient pool. Secondly, the major limitation is the uncertainty to determine whether patients who achieved remission remained in the same state or experienced disease progress in future. However, despite of these limitations, this study highlighted the significant role of DMARDs in treating post chikungunya inflammatory arthritis.

CONCLUSION

All patients diagnosed with Chikungunya viral infection are recommended to follow over a period of weeks to months in order to evaluate the development of inflammatory arthritis. Based on our results, we concluded that DMARDs have a remarkable role in treating post CHIK inflammatory arthritis and reducing the disease progression. Due to lack of enough clinical evidence, duration of the therapy has yet not been decided.

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ETHICAL APPROVAL: This study was approved by the research ethical committee of Jinnah Medical College Hospital.

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