Current Medicine Research and Practice 9 (2019) 58–64

Contents lists available at ScienceDirect

Current Medicine Research and Practice

journal homepage: www.elsevier.com/locate/cmrp

Review Article

Chikungunya infection – past to future

Sairam Bashyam*, Atul Gogia, Atul Kakar, S.P. Byotra

Department of Medicine, Sir Ganga Ram Hospital, New Delhi, India

ARTICLE INFO

Article history:
Received 29 January 2019
Received in revised form
15 March 2019
Accepted 18 March 2019
Available online 18 April 2019

Keywords:
Chikungunya
Pathogenesis
Clinical features
Vaccine

ABSTRACT

Chikungunya virus is an arthritogenic virus belonging to Alphaviridae group. The virus usually circulates in a sylvatic cycle between mammalian primates and *Aedes* mosquito. Outbreaks occur when mosquitoes bite and infect humans. From the first outbreak in early 1950s in Tanzania to the recent outbreak in New Delhi in 2016, a lot has been learnt about this virus. Outbreaks in the later part of 20th century and the 21st century have proven that the virus not only causes debilitating joint pains but also so many systemic symptoms, which were previously not recognized. The recent outbreak in New Delhi even led to mortality that was confirmed by several other studies in the recent past in different parts of the world. Similar to the virus, science in this field has also evolved much after the Tanzania outbreak. Now, we have enzyme-linked immunosorbent assays and polymerase chain reactions to detect this virus in blood. These modalities are quicker and more sensitive and specific. In recent times, physicians have started using nonsteroidal antiinflammatory drugs and disease-modifying antirheumatic drugs to treat joint pains. Several studies have come up to establish a proper protocol for treatment of the chronic joint pains, which is still the most common complication of this disease. Here, in this review, we have talked about the various outbreaks in the past, how the understanding of this disease has evolved, and about the new areas of research regarding this disease.

1. Introduction

Chikungunya virus (CHIKV) is an arthritogenic virus belonging to the Semliki forest antigenic group of the genus *Alphaviridae*, Togaviridae family.[1] Mosquitoes such as *Aedes aegypti* and *Aedes albopictus* predominantly transmit the virus. Chikungunya fever was first documented in Tanzania in early 1950s after a dengue-like illness with severe joint pains was observed.[2] Quickly, cases were identified across the world, making the infection a global issue.

The virus usually circulates in a sylvatic cycle, between mammalian primates such as chimpanzees, monkeys, and baboons and the *Aedes* mosquito. Outbreaks occur when the mosquito bites and infects a human. Since the year 2000, the scale of outbreak has increased dramatically, resulting in the spread of virus to previously nonendemic regions of the world.[3]

The disease is a self-limiting viral illness; however, debilitating joint pains may persist for months. Observations of chikungunya outbreaks in several countries of the world have shown that atypical presentations of the disease are not infrequent. There are reports of neurological involvement, hepatic failure, renal failure, and even death.[4,5]

Arthritis is the most common long-term complication that has been observed. Apart from joint involvement, neuralgia, myalgia, fatigue, hair loss, depigmentation, and depression are some of the long-term complications that a chikungunya-infected individual may face.[6]

Previously, World Health Organization (WHO) clinical criteria were used for the diagnosis. With the growth of molecular biology, technologies such as enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) have brought about a great change in diagnostic medicine. We have chikungunya real-time PCR (RT-PCR)–based and ELISA-based serological testing to confirm the diagnosis. These new modalities are quicker and easier to use and have very good sensitivity and specificity.[7]

Treatment is reassurance of patients and usually supportive care. A liberal use of analgesics including nonsteroidal antiinflammatory drugs (NSAIDs) is often required. In long-standing cases, a physician may use disease-modifying antirheumatic drugs (DMARDs) and steroids. But, data on usage of these drugs and the outcome are sparse.

In 2016, New Delhi, the capital city of India, experienced a major outbreak. A variety of clinical features, including few deaths, has been observed during the outbreak. Mortality due to chikungunya infection has been recorded in few studies in literature.[8]

CHIKV infection has an acute phase, which is typically febrile arthralgia with rashes. In few instances, other organ systems may

* Corresponding author.
E-mail address: sairam.b1992@gmail.com (S. Bashyam).

https://doi.org/10.1016/j.cmrp.2019.03.006
2352-0817

also be affected, which may be either a transient effect or a permanent defect. Chronic phase of the illness leads to incapacitating arthralgia but may also have effects on other systems.

2. Epidemiology of the virus

CHIKV was first isolated in 1952 in Tanzania.[2] But, reports of febrile arthralgia outbreaks are available since 1700 in the Caribbean island. These outbreaks were previously attributed to dengue infection by locals, which were then referred to as "break bone fever." In 1827-28, an outbreak of febrile illness occurred on the islands of Santa Cruz and St. Thomas in West Indies. Stedman noticed that the illness affected almost every person in the household, had low mortality rate, and was associated with joint pains, which prolonged for weeks after the acute phase. He reported the disease to be a bit different than the classic break bone fever (modern-day dengue fever).[9]

However, it is believed that the virus originated in Africa and spread to Asia and subsequently to the world. The earliest outbreak of this disease in Asia was in 1954.[10] Subsequent outbreaks were reported in parts of southern and southeast Asia. Genetic analyses of strains have identified three different lineages that are responsible for these outbreaks: West African lineage, East Central South African (ECSA) lineage, and Asian lineage.[11]

Since 2000, the frequency of outbreak has increased and the severity of the disease has also been increased than previously reported. In 2004, a strain that belonged to ECSA lineage caused a major outbreak in Kenya and Indian Ocean islands.[12] Concurrently, another major outbreak occurred in India in 2006. India faced its first major outbreak of this disease after 32 years.[13] There were differences in the epidemic strains of those that caused outbreaks in Indian Ocean and those that caused outbreaks in India. Both the lineages were likely to have been transmitted by the mosquito vector *Aedes albopictus*. In 2006, the virus was found to have gained a point mutation (E1-A226V), which aided the virus to adapt and replicate continuously inside the vector.

3. Pathogenesis

Acute phase of the infection is when the viral titer is high in blood, resulting in viremia. RT-PCR can be used to detect the virus easily during this phase. Patients infected with CHIKV develop a robust antibody response, and IgM concentration becomes detectable within a few days of infection.[14] IgG starts developing after about 2 weeks of infection and is known to persist for at least 21 months or even for years after infection.[15] They put up a strong immune protection against the virus and prevent development of symptoms in the event of second infection with chikungunya. The clinical symptoms of this disease are mainly due to the inflammatory response to this viremic phase. It coincides with elevation of immune mediators followed by infiltration of immune cells into the joint space and tissues.

Patients usually exhibit high concentration of circulating chemokines and cytokines.[16] The proinflammatory cytokines (interferon [IFN] α, IFN γ, and interleukin [IL]-6), antiinflammatory cytokines (IL-4, IL-10, and IL-1 receptor antagonist), and monocyte chemoattractant protein 1 (MCP-1) are to be elevated. Fibroblasts and macrophages seem to be the target dendritic cells. There is evidence of intense synovitis, periarticular enthesitis, and tendonitis.[17]

T cells play a major role in chikungunya-related arthritis. The number of circulating activated and effector T cells increased in patients with persistent chikungunya and plays a major role in pathogenesis of chikungunya-induced arthritis. Natural killer (NK) cells have also been increased in the peripheral blood of infected individuals with persistent arthritis as compared with healthy controls. This also suggests the possible role of NK cells in the pathogenesis of chronic phase of disease.[18] The virus also affects human osteoblasts, producing a cytopathic effect resulting in an erosive joint disease.[19]

At least there are three hypotheses to explain the chronic arthritis that is known to prevail after the acute phase of illness:

1. Persistence of the infectious virus in tissues, keeping the immune activation alive for months
2. Persistence of viral nucleic acid which triggers the immunopathology
3. Clearing of virus but persistence of immune activation that has already been triggered

However, additional studies are warranted to distinguish these intriguing possibilities that in turn may aid in developing effective therapeutics in future.

Animal studies have given us considerable insight into the disease. In 2010, Labadie et al.[20] injected the CHIKV, isolated from the reunion islands, into macaques. The animals developed similar clinical signs to humans. During acute phase, huge amount of viral nucleic acids were found in the spleen, lymph nodes, and liver and lesser amount in the cerebrospinal fluid (CSF), skin, muscles, and joints. Some of these macaques developed features of meningoencephalitis, and few even died.[20]

Chen et al.[21] reported the use of bindarit, a monocyte chemotactic protein inhibitor, to control osteoclastogenesis in chikungunya-infected mice and hence prevent bone erosions. They injected the virus into the foot pad of mice and observed that there was a severe reduction in the tibial bone density. They also found that the ratio between receptor activator of nuclear factor-κB and osteoprotegerin was affected, leading to an imbalance between osteoclasts and osteoblasts that resulted in bone resorption.[21]

Some studies have also identified a dual role for CCR2 macrophages. These molecules are believed to cause inflammatory response in the foot pad of mice during the acute phase of the disease. Contradictorily, these molecules also act as antiinflammatory macrophages protecting the animal from extensive bony erosions. Their absence resulted in neutrophilic infiltration of skeletal joints and bone erosions.[22]

These animal studies also hypothesize that both innate immunity and adaptive immunity play a role in CHIKV infection. Innate immunity helps during the acute phase, whereas adaptive immunity helps in the chronic phase. They have also provided with indirect evidence to support their hypotheses.

Musculoskeletal inflammation in chikungunya was exacerbated in the absence of STAT-1 signaling and type-1 interferon receptor signaling. Signal transducer and activator of transcription 1 (STAT-1) and few other receptors, such as retinoic acid inducible gene 1 (RIG-I)/melanoma differentiation associated protein 5 (MDA-5), play an important role in production of IFN-α and IFN-β in response to chikungunya infection. Rudd et al.[23] showed that any defect in these signaling pathways prolong inflammatory process of acute chikungunya infection.

Role of $CD4^+$ T cells and class-II major histocompatibility complex (MHC) has also been evaluated in some studies. They showed that CD-4+ T cells−knockout mice showed considerable reduction in the foot pad swelling after the injection of CHIKV.[24] However, viremia in these $CD4^+$ T cells−knockout mice was still under control, indicating a possible role of T-cell−independent antibody response to minimize viral replication.[24]

Chronic chikungunya infection of RAG2−/− mice showed viral nucleic acid to be persistent in joint spaces and associated histopathological evidence of arthritis, synovitis, and enthesitis.

Monoclonal antibody therapy in these mice was efficacious only in clearing the virus but not in preventing its persistence in joint spaces.[25] Together, these findings suggest a protective role of adaptive immunity in chronic disease process.

To evaluate vertical transmission of CHIKV, pregnant nonhuman primates were inoculated subcutaneously with the virus. Vertical transmission was not seen. However, infected neonates were demonstrated in few instances, suggesting the transmission to have occurred during delivery rather than in utero.[26]

Age-related immunity has also been demonstrated with these nonhuman primates. Adult primates (aged 6–13 years) were compared with aged primates (aged 17 years or more). These studies showed immune senescence affect both the immune and adaptive immunity response to the CHIKV infection.[27]

4. Clinical profile

The onset is usually similar to that of any other viral febrile illness. However, along with fever, chills, and malaise, these patients also experience intense joint pains and stiffness. Lower limbs are predominantly involved. Most patients recover from this acute phase within 2–4 days. However, after viral infection, weakness and malaise may persist even for 10 days. In rare instances, there are patients who recover over a period of one month. Clinical differentiation from dengue infection is very difficult or close to impossible. However, severe joint pains, stiffness, and puffy joints, especially that of the lower limbs, may indicate CHIKV infection. Dengue fever – classically called the break bone fever – may present with severe backache and generalized body aches. Appropriate laboratory workup is mandatory.

There is no definitive evidence regarding which joint is commonly affected or how long does the acute phase last. In early 1980s, Brighton et al.[28] conducted a retrospective cohort study with 107 subjects of CHIKV infection in South Africa. They concluded that wrists and ankles are most commonly affected, followed by knees and then the small joints of hands and feet. However, there are other studies that suggest that knee joint is the most frequently affected joint.[29]

Apart from the joint pain, patients may also have complaints of headache, painful eyes, and rashes during the acute phase. The rash usually appears 5–7 days after the infection and may last up to a week. It may or may not be associated with itching. Chopra et al.[29] reported that the elderly and children are prone for developing rashes. However, their study reported only a few children who showed faint blush on cheeks.[44] Another study conducted in India reported that rashes were predominantly seen in female population. They reported almost 50% of their study population to have rashes.[30]

Although there are enough case reports and studies suggesting cutaneous manifestations of chikungunya fever, there is no classical clinical picture that serves as a specific marker for the disease. Uncommonly, CHIKV may affect other systems also. Brighton et al.[28] showed that in their study, 21% of the subjects had gastrointestinal symptoms, 5% had cardiac involvement, and 12% had neurological involvement.

Alphaviruses are neurotropic, and there are several reports of CHIKV causing encephalitis and other neurological complications. Wadia[31] recorded the neurological complications of chikungunya after the outbreak in Pune, India. He showed encephalopathy in 47%; myelopathy in 45%; neuropathy in 58%; combined encephalopathy and myelopathy in 9%; encephalopathy and neuropathy in 11%; myelopathy and neuropathy in 16%; encephalopathy, myelopathy, and neuropathy in 12%; carpel tunnel syndrome in 13%; and retinopathy in 3%. He described a unique magnetic resonance imaging finding – hyperintense scattered dots in some patients with encephalitis.[31]

There are records of patients presenting with Guillain-Barre syndrome (GBS) such as ascending flaccid paralysis. But, unlike GBS, these patients responded poorly to plasmapheresis and steroids. Neurological complications had a male preponderance. CSF showed IgM response and virus RNA in few patients. Wadia,[31] in his case series, reported that 10 patients with encephalitis died. Autopsy was carried out in only 1 patient, which failed to demonstrate the virus. However, there is some evidence of virus in the brain of an aborted fetus whose mother was affected with CHIKV. This suggests not only a neurotropism but also a possibility of vertical transmission of the disease.[4,31]

Previously, chikungunya was considered a self-limiting, nonfatal viral infection. However, the mind-set changed after the outbreak in La-reunion Island in 2005. Mortality rate of 0.1% was recorded during the outbreak.[4] The rate was higher (about 10%) when only atypical infections were considered.[4] These included systemic manifestations of the disease. A study conducted in Ahmedabad compared chikungunya outbreak and change in mortality rate in the city of Ahmedabad during the outbreak. According to the results of that study, 2944 extra deaths were recorded in the city during the outbreak (2005-06). The study showed out of a randomly chosen 154 patients, 84 were positive for CHIKV infection, thus calculating the estimated case fatality rate to be 11.9%.[32] The authors have described a similar result when they retrospectively analyzed mortality during 2016 chikungunya outbreak in India. In this single-centered study, the case fatality rate among the admitted patients of chikungunya was 9.5%.[33]

Other acute complications that have been reported include diarrhea, nausea, vomiting, abdominal pain, hepatitis, seizures, myocarditis, pericarditis, iridocyclitis, thrombocytopenia, and hemorrhage. Maternal-fetal transmission was also reported when a new borne was identified to be positive for chikungunya infection. A recent case reports the virus to have precipitated antiphospholipid antibody syndrome in a patient with lupus.[34]

5. Postchikungunya rheumatism and arthritis

This entity, postchikungunya rheumatism and arthritis, shortly referred to as PCRA, has become a major differential diagnosis of many articular disorders in clinical medicine and rheumatology.

Persistent joint pain has been reported in 10% in literature. However, the recent outbreaks result in a greater number of PCRA. Previously, chikungunya-related joint involvement was characterized under chronic erosive arthritis, but now, it seems to be an overlap or preexisting rheumatoid arthritis. The study during the epidemic of La-reunion Island showed that almost 60% people who were enrolled in the study suffered from arthralgia at the end of 36 months.[8] Hospital-based tertiary center studies suffer from severe limitation in terms of selection bias and retrospective study. Population-based studies are scarce and difficult to perform.

A rural population study was conducted in Sholapur district, which was sponsored by the Indian Council of Medical and Research (ICMR). It was a prospective study conducted immediately after the 2006 outbreak. A total of 509 cases were identified. Almost 65% of the cases recovered in 4 weeks. Of the rural community, 4.1% suffered from persistent pain after 1 year. This fell to 1.6% at the end of 2 years. Serum IL-6 and IL-13 remained elevated for longer periods not only in patients with chronic arthritis but also in several others after recovery.[29] This indicates the possibility of persistent immune activation even after clinical recovery.

A similar study in South India reported a large number of patients with PCRA in addition to a wide spectrum of enthesitis, tenosynovitis, and rotator cuff syndrome. It is logical to conclude that PCRA in a tertiary care center does not reflect the true burden of the community.[35]

The 2006 epidemic brought about a great change in the spectrum of PCRA. Chopra et al.[36] described 5 patterns of rheumatological disorders within 6 months of acute infection. There was no gender preponderance. Only two patients (5.4%) had rheumatoid factor positivity. Anti-cyclic citrullinated peptide (CCP) was positive in almost 12%. Antinuclear antibody was positive in half of the population. None of the patients with inflammatory arthritis showed bony erosions in X-rays. Few patients showed periarticular inflammation and joint swelling. Undifferentiated inflammatory arthritis is usually asymmetrical oligoarthritis. Lower limbs were predominantly involved. Soft-tissue involvement was in the form of fibromyalgia, backache, and calf pain. The knee was the most commonly affected joint sometimes showing degenerative changes including crepitus. Sixty-one patients with previous rheumatologic disorders experienced a flare-up, and few other rheumatologic disorders were documented for the first time soon after the virus infection.[36]

Long-term follow-up data of PCRA are fully lacking. Several studies have attempted to find out the number of days or perhaps months the symptoms may last. The case report by Bank et al.[37] reported that their patient had joint pain for around 3.5 months; however, myelopathy and weakness persisted for at least 6 months, while neuropathy lasted further longer. Timeline is just one aspect of research, while there are much more concerns regarding this postchikungunya rheumatism.

Another way of looking at it is the risk factors to develop long-term complication of chikungunya infection. There are several studies in literature that suggest possible risk factors to develop PCRA. One of them quoted age above 40 years to be a major risk factor of developing chronic debilitating arthritis. As per the results of the study, mean age was found to be 57.4 years above, in which the symptoms persisted longer,[38] whereas another study reported that female sex and symmetrical joint involvement were related to persisting long-term joint pains.[39]

Finally, the big question trending among the rheumatologists is whether PCRA has a specific true form for itself. Is there a classic pattern of joint involvement, specific clinical features, extra-articular manifestations, and laboratory alterations? The answer is yet to be found out. CHIKV markers have been identified in the synovium of patients with chronic arthritis.

There are rheumatologists who believe chikungunya may play a crucial role in the future of rheumatic diseases. It may be a trigger for several existing rheumatic diseases and many more yet to be discovered. Indeed, chloroquine trial showed that it is the persistence of the virus or its fragments that contribute to PCRA and not autoantibodies.[40] But, there seems to be a distinct form of PCRA that resembles rheumatoid arthritis – the pattern of joint involvement, soft-tissue inflammation, absence of rheumatoid factor (RF), or anti-CCP. This form of PCRA is very relentless and progressive and may lead to bony erosions and severely degenerative end-stage arthritis.

6. Diagnosis

Clinical diagnosis is easier during the times of outbreak. But, it is always challenging to make a clinical diagnosis in an isolated case. In our setting, it has to be differentiated from dengue fever. Dengue fever may present with fever with rashes and severe backache, while peripheral joint pain may point toward chikungunya. Hemodynamic instability and shock are commoner in dengue infection than in chikungunya infection. Initial evaluation may show leucopenia in both the viral infections. Thrombocytopenia may be mild in chikungunya, while a severe thrombocytopenia favors dengue fever.

Previously, diagnosis was mainly based on clinical criteria set by the WHO (Table 1).

6.1. Virus isolation and culture

This can be performed by intracerebral inoculation of mice or mosquito inoculation. There are other *in vitro* techniques such as mosquito-based cells lines including C6/36 or mammalian cell lines including BHK-21, Vero, and HeLa cells. These *in vitro* techniques have proved to be comparable with that of *in vivo* techniques. The cytopathic effects should be checked with chikungunya antiserum, and it may take up to one to two weeks for confirmation of results. Virus isolation and culture are performed only in BSL-3 laboratories.[42]

6.2. Molecular diagnosis

RT-PCR or nested PCR combination amplifying fragment of E2 gene can make specific diagnosis. Newer techniques are nowadays targeting nsP-1 and envelope E-1 gene for rapid diagnosis and genotyping at the same time. A very sensitive and specific one-step Taqman RT-PCR has been introduced for quick diagnosis and rapid quantification of virus in clinical samples and cell culture supernatant.[43] Real-time loop-mediated isothermal amplification assay (RT-LAMP) is another technique that has been introduced for a rapid molecular detection.[44]

6.3. Serological diagnosis

To make a serological diagnosis, 10–15 ml of blood sample is required. Serum should be separated. Two samples are to be collected: Acute phase serum sample, collected immediately after the onset of illness, and convalescent phase serum, collected after 10–14 days. If the laboratory is nearby, the specimen should not be frozen and should be transported at 4 °C. Only if the testing cannot be performed immediately, should the serum specimen be separated and then stored and shipped frozen.

Serological diagnosis can be made with IgM or IgG antibody titer. It is enough to demonstrate IgM only in the acute phase sample. ELISAs and immunochromatographic tests are the currently available techniques to detect these antibodies. IgM titers start declining within 3–6 months. The National Institute of Virology (NIV), Pune, India, has developed a test kit for in-house use.

Hemagglutination inhibition (HI) antibodies are not very commonly used for diagnosis. They usually appear in the blood of the infected after the cessation of viremia. They are useful after 5–7 days of illness. The CHIKV antigen for HI test is available from the NIV, Pune[45] (Table 2).

Table 1
Case definition for chikungunya fever.[41]

- Clinical criteria: Acute onset of fever >38 °C and severe arthralgia/arthritis not explained by other medical conditions.
- Epidemiological criteria: Residing or having visited epidemic areas, having reported transmission within 15 days before the onset of symptoms.
- Laboratory criteria: At least one of the following tests in the acute phase
  - Virus culture, isolation.
  - Presence of viral RNA by RT-PCR.
  - Presence of virus-specific IgM antibodies in single serum sample collected in acute or convalescent stage.
  -Fourfold increase in IgG antibody values in samples collected at least three weeks apart.
- On this basis, cases are to be categorized as follows:
- Possible case: A patient meeting clinical criteria.
- Probable case: A patient meeting both clinical and epidemiological criteria.
- Confirmed case: A patient meeting the laboratory criteria, irrespective of the clinical presentation.

RT-PCR = real-time polymerase chain reaction.

Table 2
Pros and cons of various diagnostic tests for chikungunya virus.

Tests	Pros	Cons
Virus isolation and culture	• Gold standard for diagnosis of chikungunya infection	• Requires facilities and skills • Also requires biosafety level 3 containment
Molecular diagnosis including RT-PCR and RT-LAMP	• Highly sensitive and specific • Rapid diagnosis	• Reagents and equipment are very costly for widespread use.
Antigen detection tests	• Not yet commercially available	• CHIKV antigen commercial assays are not widely available. Performance characteristics are not clearly defined. • Also requires biosafety level 3 containment during preparation
Serological tests to detect antibody titer by ELISA or ICT	• Widely performed • Easier to use • Relatively cheaper	• Cross-reactivity with other alphaviruses. • Single raised IgM may indicate recent past infection rather than acute infection. • Sensitivities vary widely, >80% after 1 week of clinical presentation, less useful for clinicians

PCR = polymerase chain reaction; RT = reverse transcription; LAMP = loop-mediated isothermal amplification assay; CHIKV = chikungunya virus.

The WHO recommends the following characteristics for an ideal testing method: sensitive, specific, user friendly, affordable, rapid, robust to use in different climates, devoid of equipment, and transportable. Newer innovations such as RT-LAMP fulfill most of the criteria. They can be transported, are user friendly, and yet have sensitivity and specificity comparable with those of other molecular techniques. However, patients who are acutely ill would reach the hospital within the first few days of illness and the most ideal test would be detection of antigen or RNA of the virus. Hence, the more realistic aim is to develop antigen detection assays that could be easily transported to the needful and rural areas, which are prone to outbreaks. Also, these assays should be tested rigorously with samples from different clinical setting including infections caused by different CHIKV strains.[46]

6.4. Treatment

There are no specific drugs approved for treatment of chikungunya infection at present. Treatment is symptomatic and empirical. Some treatment guidelines have been published, but evidence-based medicine does not favor them. Symptomatic treatment includes providing assurance and comfort to patients. NSAIDs and other analgesics can be used for arthritis. There is no specific NSAID that should be prescribed, but fast-acting NSAIDs, such as diclofenac or naproxen, will be better. Some patients may also need tramadol for their pain. It is important to monitor for their side effects, especially in elderly with other comorbidities. Chloroquine is one drug that has been evaluated extensively. At least one French trial fails to show its efficacy in treatment of acute phase of infection.[28]

There is no compelling evidence to report that DMARDs may be helpful in PCRA. However, based on clinical judgment, steroids or DMARDs may be used in cases of severe arthritis. There have also been situations in which patients needed intravenous steroids followed by tapering doses of oral steroids to control their intense pain. There are a few small case series, which claim that biologicals can be used when DMARDs fail.[47] But, there is neither convincing proof for the claim nor any long-term data supporting the statement.

Anti-CHIKV drugs has been developed and evaluated in animal studies. Bindarit, an inhibitor of MCP-1, is one such drug. Although the drug showed promising results in animal studies, tests on humans show no such effects. Other compounds that are being investigated include phenothiazines and flavaglines.[48] Ribavirin has shown some promising results *in vitro*. Animal studies have also shown that when ribavirin is synergized with doxycycline, inflammation and viral load can be controlled.[49] Mycophenolic acid was shown to be more potent than ribavirin in controlling replication of virus in cellular studies.[50] CHIKV nonstructural protein nsP2 is a helicase and a protease, and experiments are being conducted to find out if any of the known protease has effect on this alphavirus.[51]

Table 3
Some examples of investigational strategies under development for treatment of chikungunya virus infection.[53]

Therapeutic	Mechanism	Data	
		In vitro	*In vivo*
Chloroquine	• Inhibits fusion of CHIKV E1 protein with the endosomal membrane	• Inhibited CHIKV infection in Vero A cells	• No efficacy in clinical trials in patients infected with CHIKV
siRNA-targeting CHIKV genes	• Inhibits protein synthesis	• Inhibited CHIKV replication in Vero-E6 cells (>90%)	• Inhibited CHIKV replication in mice when administered 3 d after infection
Ribavirin	• Inhibits viral genome replication by depleting guanosine triphosphate	• Inhibited CHIKV replication in Vero cells • Synergistic inhibitory effect in combination with IFN-a2b and doxycycline	• Reduced the viral load and inflammation in infected ICR mice when combined with doxycycline
Favipiravir (T-705)	• Inhibits viral genome replication	• Inhibited CHIKV- induced cytopathic effect in Vero A cells	• Reduced mortality of infected AG129 mice and protected from neurologic disease
Monoclonal antibody C9	• Binds CHIKV E2 glycoprotein	• Neutralized CHIKV pseudovirions in HEK293T cells and CHIKV in Vero cells	• 100% survival of CHIKV-infected mice when given at 8 or 18 h after infection

CHIKV = chikungunya virus; siRNA = small interfering ribonucleic acid.

Based on the available evidence, Brito et al.[52] suggested a protocol of treatment, in which they suggested that the drug of choice depends on the visual analog scale (VAS) and the duration of the disease. During acute phase, when the pain is mild (VAS < 3), paracetamol is sufficient. In moderate to severe pain, paracetamol and ibuprofen or paracetamol and tramadol combination can be used. If pain does not subside, neuropathic pain has to be considered and amitriptyline may be used for treatment. Postacute phase (after 22 days of acute infection) patients shall be prescribed NSAIDs. If the pain persists, corticosteroids can be given; prednisone is preferred. In case of inflammation such as tenosynovitis, bursitis or capsulitis intravenous corticosteroid shall be given. When pain persists more than 3 months, DMARDs can be given. Physiotherapy, orthotics to rest the inflamed joints, synovial fluid drainage, and topical NSAIDs or patch are the other available options. Monoclonal antibodies to envelope proteins E1 and E2 have been used to protect mice and other nonhuman primates from CHIKV infection. However, their use in already infected animals is unclear (Table 3).

6.5. *Is vaccine a possibility?*

Discovery of chikungunya vaccine have been attempted ever since the first outbreak. The first vaccine that was discovered was in 1960, which was formalin-inactivated virus preparation.[54] After its failure, attenuated vaccines were developed. One such vaccine developed with the isolate from La-reunion outbreak showed encouraging results in animal studies.[55] Virus-like particles including capsid and envelope proteins were immunogenic in mice, inducing protective neutralizing antibodies. These virus-like particle vaccines have successfully been used in human trials, and no adverse effects have been documented so far.[56] Nonalpha virus vectors carrying CHIKV proteins, DNA-based vaccine expressing CHIKV proteins, and subunit vaccine with recombinant E2 and E1 protein antigens are some of the possibilities being investigated.

Conflicts of interests

None.

References

1. Strauss JH, Strauss EG. The alphaviruses: gene expression, replication, and evolution. *Microbiol Rev*. 1994;58:491–562.
2. Robinson MC. An epidemic of virus disease in Southern Province, Tanganyika territory, in 1952–1953. *Trans R Soc Trop Med Hyg*. 1955;49:28–32.
3. Diallo M, Thonnon J, Traore-Lamizana M, Fontenille D. Vectors of chikungunya virus in Senegal: current data and transmission cycles. *Am J Trop Med Hyg*. 1999;60:281–286.
4. Joubert JJ, Prozesky OW, Lourens JG, Theron JW, Swanevelder C, Meenehan GM. Prevalence of hepatitis virus and some arbovirus infections in Kavango, northern SWA/Namibia. *S Afr Med J*. 1985;67:500–502.
5. Josseran L, Paquet C, Zehgnoun A, et al. Chikungunya disease outbreak, reunion island. *Emerg Infect Dis*. 2006;12:1994–1995.
6. Soumahoro MK, Gérardin P, Boëlle PY, et al. Impact of Chikungunya virus infection on health status and quality of life: a retrospective cohort study. *PLoS One*. 2009;4. e7800.
7. Shukla J, Khan M, Tiwari M, et al. Development and evaluation of antigen capture ELISA for early clinical diagnosis of chikungunya. *Diagn Microbiol Infect Dis*. 2009;65:142–149.
8. Schilte C, Staikovsky F, Couderc T, et al. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. *PLoS Neglected Trop Dis*. 2013;7. e2137.
9. Carey DE. Chikungunya and dengue: a case of mistaken identity? *J Hist Med Allied Sci*. 1971;26:243–262.
10. Rao TR. Immunological surveys of arbovirus infections in South-East Asia, with special reference to dengue, chikungunya, and Kyasanur Forest disease. *Bull World Health Organ*. 1971;44:585–591.
11. Powers AM, Brault AC, Tesh RB, Weaver SC. Re-emergence of chikungunya and o'nyong-nyong viruses: evidence for distinct geographical lineages and distant evolutionary relationships. *J Gen Virol*. 2000;81:471–479.
12. Sergon K, Yahaya AA, Brown J, et al. Seroprevalence of chikungunya virus infection on Grande Comore Island, union of the Comoros, 2005. *Am J Trop Med Hyg*. 2007;76:1189–1193.
13. Arankalle VA, Shrivastava S, Cherian S, et al. Genetic divergence of chikungunya viruses in India (1963–2006) with special reference to the 2005–2006 explosive epidemic. *J Gen Virol*. 2007;88:1967–1976.
14. Seymour RL, Adams AP, Leal G, Alcorn MDH, Weaver SC. A rodent model of chikungunya virus infection in RAG1 -/- mice, with features of persistence, for vaccine safety evaluation. *PLoS Neglected Trop Dis*. 2015;9. e0003800.
15. Kam Y-W, Lee WWL, Simarmata D, et al. Longitudinal analysis of the human antibody response to chikungunya virus infection: implications for serodiagnosis and vaccine development. *J Virol*. 2012;86:13005–13015.
16. Chirathaworn C, Poovorawan Y, Lertmaharit S, Wuttirattanakowit N. Cytokine levels in patients with chikungunya virus infection. *Asian Pac J Trop Med*. 2013;6:631–634.
17. Teng T-S, Kam Y-W, Lee B, et al. A systematic meta-analysis of immune signatures in patients with acute chikungunya virus infection. *J Infect Dis*. 2015;211:1925–1935.
18. Miner JJ, Aw Yeang HX, Fox JM, et al. Brief report: chikungunya viral arthritis in the United States: a mimic of seronegative rheumatoid arthritis. *Arthritis Rheum*. 2015;67:1214–1220.
19. Noret M, Herrero L, Rulli N, et al. Interleukin 6, RANKL, and osteoprotegerin expression by chikungunya virus-infected human osteoblasts. *J Infect Dis*. 2012;206:455–457.
20. Labadie K, Larcher T, Joubert C, et al. Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. *J Clin Investig*. 2010;120:894–906.
21. Chen W, Foo S-S, Taylor A, et al. Bindarit, an inhibitor of monocyte chemotactic protein synthesis, protects against bone loss induced by chikungunya virus infection. *J Virol*. 2015;89:581–593.
22. Poo YS, Nakaya H, Gardner J, et al. CCR2 deficiency promotes exacerbated chronic erosive neutrophil-dominated chikungunya virus arthritis. *J Virol*. 2014;88:6862–6872.
23. Rudd PA, Wilson J, Gardner J, et al. Interferon response factors 3 and 7 protect against chikungunya virus hemorrhagic fever and shock. *J Virol*. 2012;86:9888–9898.
24. Teo T-H, Lum F-M, Claser C, et al. A pathogenic role for CD4+ T cells during chikungunya virus infection in mice. *J Immunol*. 2013;190:259–269.
25. Hawman DW, Stoermer KA, Montgomery SA, et al. Chronic joint disease caused by persistent chikungunya virus infection is controlled by the adaptive immune response. *J Virol*. 2013;87:13878–13888.
26. Chen C-I, Clark DC, Pesavento P, et al. Comparative pathogenesis of epidemic and enzootic chikungunya viruses in a pregnant Rhesus macaque model. *Am J Trop Med Hyg*. 2010;83:1249–1258.
27. Messaoudi I, Vomaske J, Totonchy T, et al. Chikungunya virus infection results in higher and persistent viral replication in aged rhesus macaques due to defects in anti-viral immunity. *PLoS Negl Trop Dis*. 2013;7:e2343.
28. Brighton SW, Prozesky OW, De La Harpe AL. Chikungunya virus infection. A retrospective study of 107 cases. *S Afr Med J*. 1983;63:313–315.
29. Chopra A, Anuradha V, Ghorpade R, Saluja M. Acute Chikungunya and persistent musculoskeletal pain following the 2006 Indian epidemic: a 2-year prospective rural community study. *Epidemol Infect*. 2012;140:842–850.
30. Riyaz N, Riyaz A, Rahima, Latheef A, Anitha PM. Cutaneous manifestations of chikungunya during a recent epidemic in Calicut, North Kerala, South India. *Indian J Dermatol Venerol Leprol*. 2010;76:671–676.
31. Wadia RS. A neurotropic virus and a neurotropic amino acid. *Ann Indian Acad Neurol*. 2007;10:198–213.
32. Pan American health organization. *Preparedness and Response for Chikungunya Virus: Introduction in the Americas*. Washington DC: PAHO; 2011. cited 2018 Dec 18] Available from: https://www.paho.org/hq/index.php?option=com_topics&view=article&id=343&Itemid=40931Data.
33. Gogia A, B S, Kakar A. Chikungunya: a mortality report. *Open Forum Infect Dis*. 2017;4:S518.
34. Betancur JF, Navarro EP, Bonilla BJH, et al. Catastrophic antiphospholipid syndrome triggered by fulminant chikungunya infectionin a patient with systemic lupus erythematosus. *Arthritis Rheum*. 2016;68:1044.
35. Mathew AJ, Goyal V, George E, Thekkemuriyil DV, Jayakumar B, Chopra A. Rheumatic musculoskeletal pain and disorders in a naïve group of individuals 15 months following a chikungunya viral epidemic in South India: a population based observational study. *Int J Clin Pract*. 2011;65, 1036-12.
36. Chopra A, Venugopalan V. Persistent rheumatic and musculoskeletal disorders at one year post chikungunya epidemic in south Maharashtra a rural community based observational study with special focus on naïve persistent rheumatic musculoskeletal cases and selected cytokine expression. *Indian J Rheumatol*. 2011;6:5–11.
37. Bank AM, Batra A, Colorado RA, Lyons JL. Myeloradiculopathy associated with chikungunya virus infection. *J Neuroviral*. 2016;22:125–128.
38. Gerardin P, Fianu A, Malvy D, Mussurd C, Boussaid K. Perceived morbidity and community burden after Chikungunya outbreak: the Telechik Survey, a population based cohort study. *BMC Med*. 2011;9:5.
39. Essackjee K, Goorah S, Ramchurn SK, Cheeneebash J, Walker-Bone K. Prevalence of and risk factors for chronic arthralgia and rheumatoid-like polyarthritis more than 2 years after infection with chikungunya virus. *Postgrad Med*. 2013;89:440–447.

40. Chopra A, Saluja M, Venugopalan A. Chloroquine effectiveness and inflammatory cytokine response in early persistent post chikungunya musculoskeletal pain and arthritis. *Arthritis Rheum*. 2014;66:319–326.
41. World Health Organization Regional office for South-East Asia. *Guidelines for Prevention and Control of Chikungunya Fever*; 2009 [cited 2012 Jul 15]. Available from: http://www.searo.who.int/Link Files/Publication_SEA-CD-182.pdf.
42. Sarkar JK, Pavri KM, Chatterjee SN, Chakravarty SK, Anderson CR. Virological and serological studies of cases of hemorrhagic fever in Calcutta: material collected from Calcutta School of Tropical Medicine. *Indian J Med Res*. 1964;52:684–691.
43. Pastorino B, Bessaud M, Grandadam M, Murri S, Tolou HJ, Peyrefitte CN. Development of a TaqMan RT-PCR assay without RNA extraction step for the detection and quantification of African Chikungunya viruses. *J Virol Methods*. 2005;124:65–71.
44. Lakshmi V, Neeraja M, Subbalaxmi MV, et al. Clinical features and molecular diagnosis of Chikungunya fever from South India. *Clin Infect Dis*. 2008;46:1436–1442.
45. Johnston RE, Peters CJ. Alphaviruses. In: Fields BN, ed. *Fields Virology*. third ed. Philadelphia: Lippincott-Raven; 1996:843–898.
46. Banoo S, Bell D, Bossuyt P, Herring A, Mabey D. TDR Diagnostics Evaluation Expert Panel. Evaluation of diagnostic tests for infectious diseases: general principles. *Nat Rev Microbiol*. 2010;8:S17–S29.
47. Javelle E, Ribera A, Degasne I, Gauzere BA, Marimoutou C, Simon F. Specific management of post-chikungunya rheumatic disorders: a retrospective study of 159 cases in reunion island from 2006-2012. *PLoSNegl Trop Dis*. 2015;9. e0003603.
48. Pohjala L, Utt A, Varjak M, et al. Inhibitors of alphavirus entry and replication iden- tified with a stable chikungunya replicon cell line and virus-based assays. *PLoS One*. 2011;6. e28923.
49. Rothan HA, Bahrani H, Mohamed Z, et al. A combination of doxycycline and riba- virin alleviated chikungunya infection. *PLoS One*. 2015;10. e0126360.
50. Scholte FEM, Tas A, Martina BEE, et al. Characterization of synthetic chikungunya viruses based on the consensus sequence of recent E1-226V isolates. *PLoS One*. 2013;8. e71047.
51. Bassetto M, De Burghgraeve T, Delang L. Computer-aided identification, design and synthesis of a novel series of compounds with selective antiviral activity against chikungunya virus. *Antivir Res*. 2013;98:12–18.
52. Brito CAA, Von Sohsten AKA, LEitao CCS, et al. Pharmacological pain treatment in Chikungunya: a guideline. *Rev Soc Bras Med Trop*. 2016;49:668–679.
53. Abdelnabi R, Netys J, Delang L. Towards antivirus against Chikungunya virus. *Anti-viral Res*. 2015;121:62.
54. Harrison VR, Eckels KH, Bartelloni PJ, Hampton C. Production and evaluation of a formalin-killed chikungunya vaccine. *J Immunol*. 1971;107:643–647.
55. Chu H, Das SC, Fuchs JF, et al. Deciphering the protective role of adaptive immunity to CHIKV/IRES a novel candidate vaccine against chikungunya in the A129 mouse model. *Vaccine*. 2013;31:3353–3360.
56. Chang L-J, Dowd KA, Mendoza FH. Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial. *Lancet*. 2014;384:2046–2052.