Chapter

Treatment and Prevention of Chikungunya Fever: Current Status and Prospective

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Abstract

Chikungunya fever is a vector borne tropical disease that was first described in an outbreak in Tanzania. The disease is caused by Chikungunya virus (CHIKV), an alpha virus belonging to the family Togaviridae and which is transmitted from one person to another via the bite of mosquitoes. Active disease is characterized by high grade fever, pain and joint symptoms. Although debilitating at times, the disease seldom progresses to result in a serious outcome like death. There are no specific treatments for Chikungunya virus at the moment. Clinical case management is highly dependent on providing palliative care which in turn is expected to alleviate symptoms and accelerate recovery from the infection. An important element in the control of outbreaks of CHIKV infection is prevention. Preventive strategies involve initiatives like vector control, immunizations and extra care to patients with the infection. There have been several tens of researches focusing on the introduction of newer drugs and vaccines against Chikungunya. That being said, so far, no single agent has completed the entire drug or vaccine development process. Chikungunya fever is a neglected tropical disease. Although it has no specific treatment till date, the number of vaccine and drug candidates under study provides promising insights on the prospects on chikungunya treatment.

Keywords: Febrile Illnesses, Chikungunya Virus, Palliative Care and Vector Control

1. Introduction

Chikungunya fever was first described in Tanzania in the year 1952 during an outbreak in the southern part of the country. The disease is a vector borne infection transmitted by mosquitoes carrying the causative agent, Chikungunya virus (CHIKV), an RNA virus of the genus alphavirus and family Togaviridae [1]. CHIKV is transmitted to humans by bites of several species of mosquitoes, the two main species of mosquitoes transmitting the disease being *Aedes aegypti* and *Aedes albopictus* [2]. Major symptoms of the infection include fever (sudden high grade 39–40°C), muscle and joint pain, swelling (joints), headache, nausea and other minor skin reactions [3]. Deaths from severe infections are not common and if any, the deaths are usually linked to other underlying medical conditions. Persons suffering an active infection may develop debilitating joint pain that gives them a distinct curved or bent posture and this is from which the disease's name 'Chikungunya' was derived, which in the Makonde dialect means 'to be contorted or bent'.

Although Chikungunya fever occurs throughout the world, it is specifically common in the African continent. The disease is similar to many other febrile viral illnesses in terms of the clinical presentation of infected patients, thus; it can be misdiagnosed in areas where there are inadequacies of laboratory setups and testing procedures [4]. Even when it was first described as a disease in Tanzania, it was clinically indistinguishable from dengue fever [3]. For this reason, there are inaccuracies in the numbers of infections of Chikungunya reported from various setups and in many instances, it is almost impossible to come up with a reliable estimate of the prevalence of the infection.

Currently, there are no commercially available vaccines or any specific drugs to cure Chikungunya fever and existing treatments generally focus on relieving symptoms. That being said, there have been immense research throughout the years in pursuit of specific drug candidates and vaccines to target the causative agent, but yet; no single entity was made available to the world. The most effective intervention the world has been working on is to improve infection prevention strategies targeting activities ranging from vector control to prevention of mosquito bites and acquiring the infection.

This chapter provides brief highlights on the treatment approaches so far used, preventive strategies employed and promising prospective drug and vaccine candidates whose development have been underway in the past few years.

2. Management of Chikungunya fever

Management of any infectious disease generally requires meticulous examination and a differential diagnosis in order to ascertain what is being dealt with in the first place. Before starting to treat Chikungunya fever, it is of utmost importance to rule out other viral infections, like Zika virus and Dengue fever, that have similar clinical presentation. Although in its severe form Chikungunya is a debilitating illness, like all other viral illnesses, the viral load of CHIKV is lowered by the body's immune response, thus; the symptoms are self-limiting and patients usually fully recover.

There are generally two approaches into the treatment of any disease condition, namely the specific treatment that focuses on the cause of the disease and another is a non-specific intervention intended to alleviate symptoms of the disease. Today, there is no specific antiviral drug or vaccine intended for use against the CHIKV and for this reason, managing Chikungunya fever clinically is palliative, meaning it only focuses on relieving the symptoms [5]. There are various pharmacologic and non-pharmacologic approaches into doing this, the main of which are explored in the next section.

2.1 Symptomatic treatments

Symptomatic interventions generally work to alleviate the symptoms that may result from a disease condition without necessarily having to deal with the underlying cause of the disease itself. In case of Chikungunya, a number of pharmacologic and non-pharmacologic approaches may be used to alleviate symptoms of the febrile illness.

2.1.1 Non-pharmacologic palliative care

Non-pharmacologic interventions do not employ the use of active chemical entities that modify or make use of a specific biochemical and/or physiological

processes to bring about the required change and thereby alleviate a symptom. Such interventions include life style elements like dietary modifications, fluid intake and bed rest. A common symptom in patients experiencing active Chikungunya infection is generalized body weakness and lethargy, thus; adequate nourishment and rest is very important to boost the patient's immune response. Consumption of citrus fruits and the use of multivitamin supplements may also be recommended in some cases where there is loss of appetite. Taking plenty of fluids on the other hand helps the patient to stay rehydrated thereby maintaining stamina and metabolic stability. All these interventions play a vital role in optimizing the immune attack the body launches against the virus and thus not only alleviate the symptoms, but also accelerate the whole recovery process.

2.1.2 Pharmacologic palliative care

Pharmacologic interventions employ the use of specific active pharmaceutical entities which make use of specific bodily biochemical and/or physiological pathways to bring about a specific effect and thereby alleviate a symptom. The most common symptoms namely fever and joint pain can be alleviated with the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). It is a fact that all NSAIDs have anti-pyretic (body temperature lowering) and analgesic (pain relieving) properties. Despite this fact, paracetamol or acetaminophen is more commonly used to manage fever and mild pain while drugs belonging to the same therapeutic class like ibuprofen, diclofenac and naproxen are used to alleviate pain to maintain a favorable risk–benefit balance when using those medicines. Although Aspirin belongs to the NSAIDs, its use for analgesia and as an anti-pyretic agent is not recommended. This is in particular because of its blood thinning properties, giving the drug an unfavorable risk–benefit balance when used for these specific indications.

There are a number of studies debating over the use of chloroquine to treat the arthritis like symptoms of Chikungunya fever. Even if there is evidence that chloroquine is effective in managing various rheumatic joint diseases, its use for the management of Chikungunya fever related joint symptoms remains questionable. Disease-modifying anti-rheumatic drugs are also claimed to be effective in treating Chikungunya virus induced symptoms of chronic joint diseases that resemble rheumatoid arthritis in their presentation. The literature also presents other medicines like eupatorium perf, influenzinum, rhus-tox, pyroginum and cedron that are primarily utilized in south east Asia and are believed to play curative and preventive roles.

Interventions to alleviate symptoms of Chikungunya, whether non-pharmacologically or pharmacologically, are believed to be effective in improving prognosis and overall accelerating full recovery form the illness. A careful consideration should however be made when selecting an appropriate treatment, particularly a pharmacological palliative intervention, for the patient so that the risk benefit balance of using the treatment remains favorable.

2.2 Specific treatments

In principle, a specific treatment is supposed to completely cure a disease. This would mean that the treatment will precisely target the pathophysiological root cause of the disease in the case of non-infectious disease and the invading causative agent in the case of an infectious disease.

Till date, there is no single antiviral entity proven to be specifically effective against the CHIKV. There have however been several antiviral candidates under study to target the virus. With regard to active and passive immunizations against

Approach	Specific intervention	Example:
Palliative care	Non-pharmacologic treatment	**Real-time:** Dietary modification, rehydration and bed rest all play key role in boosting the immune responses against the virus and thus facilitating full recovery.
	Pharmacologic treatment	**Real-time:** The use of NSAIDs such as paracetamol or ibuprofen to alleviate fever and indomethacin or diclofenac to relieve joint pain.
Specific treatment	Antiviral drugs	**Prospective:** Specific antiviral drugs that target CHIKV by interfering with the various vital steps in the viral replication cycle such as attachment, penetration, un-coating, replication, assembly, and release.
	Therapeutic (passive) immunization	**Prospective:** The use of specific preformed antibodies that directly target the whole virus or viral coat molecules there by clearing viral particles.

Table 1.
Real-time and prospective approaches for the management of chikungunya fever.

the virus, no vaccine is commercially available for use in humans today. There are however several vaccine strategies under study and some vaccine candidates have now reached to advanced stages in the clinical development process. These candidates are however still long way from the approval step and longer way from being available in markets for consumption.

The management of Chikungunya fever is primarily palliative. Until the time when specific curative alternatives are made available, it is recommended that health practitioners make wise use of the available treatment options. Moreover, there are various recommended treatment guidelines specific to Chikungunya fever that provide clear steps on how effectively one can manage the infection [3].

Table 1 summarizes the various approaches used today and the likely to be future treatment options in the management of CHIKV.

3. Preventive measures

The prevention of disease acquirement and transmission is key to halt the spread of any infectious disease. In case of Chikungunya virus infection, prevention becomes vital to control spread especially that there are no specific treatments against the disease. There may be several preventive strategies to control the spread of Chikungunya fever. For the purpose of clarity, this section summarizes them into three major approaches namely vector control measures, immunizations and care for the already diseased persons.

3.1 Vector control and avoiding mosquito bites

Chikungunya is an arthropod borne viral infection. CHIKV is transmitted to humans by bites of several species of mosquitoes [2, 3]. The two main species of mosquitoes transmitting the disease are *Aedes aegypti* and *Aedes albopictus*. *Aedes aegypti* is commonly responsible for transmission in urban areas whereas *Aedes albopictus* has been the main vector in rural areas. These mosquitoes can be easily distinguishable from others by the presence of white markings on their limbs and a marking in the form of a lyre on the upper surface of the thorax. Recognizing

the mosquito itself is very important as it gives an insight into the possibility of the existence of an outbreak in a specific area.

The control and termination of breeding of the vector is key to the prevention of the transmission of any vector borne infection. In the control of CHIKV outbreaks, vector control through the use of larvicides and adulticides, the removal of larval habitats, limiting human-vector contact and public education is critical [6]. The measures that should be taken in vector control are similar to those used in the control of transmission of malaria. The common measures that should be taken include:

- Emptying and scrubbing, turning over, burying, covering, or throwing out items that hold water. Since mosquitoes need water to lay eggs, it is very important to cover or dry swampy spots in the surrounding of the outdoors of living places.

- Using insecticides and repellents to kill and/or keep away mosquitoes from indoors and thereby avoiding bites.

Another important measure that should be taken to control the spread of CHIKV is to avoid mosquito bites. There are a few things that can be done to avoid bites:

- Recognizing the mosquito based on its physical appearance (white markings) and being aware that unlike the mosquitoes that spread malaria which are usually active and bite during the night time, the Aedes species are active and bite during both the day and the night times.

- Sleeping under a mosquito net especially in areas where mosquito breeding rates are very high. Such places may include high humidity and swampy areas.

- Applying mosquito repellents. There are a wide variety of products that contain mosquito repellents and are available in different formulations such as lotions and creams.

Since mosquitoes have a major role in the spread of CHIKV, targeting them is key to halt the transmission cycle. Vector control comprises a set of activities, not limited to the above described, intended to minimize transmission of CHIKV and thereby the occurrence of active Chikungunya infections.

3.2 Immunization

Active immunization against specific foreign entities entering the human body has been one of the most effective strategies in the prevention of communicable diseases. Like other infectious diseases, CHIKV has been a subject of interest for many vaccine developers. There is however no vaccine that have been made commercially available for preventive immunizations against the disease.

Recent studies list a number of candidates that are under development [7, 8]. Of the candidates, there is a single vaccine that have made progress to phase three clinical trials, which seems to be the most progressing out of the rest of the candidates [9]. That being said, according to what is published in the scientific literature thus far, making a vaccine available for human use does not seem to be something that one should expect in the very near future.

S.No.	Strategy	Category	Description
1.	Vector Control	Minimizing mosquito breeding	Controlling mosquito habitats (water holes, swamps and dump areas) and use of insecticides, larvicides and adulticides to limit vector proliferation.
		Avoiding mosquito bites	Sleeping under mosquito nets, avoiding shorts and short sleeved wears during both day and night times (to minimize open exposure of the skin surface) and the application of mosquito repellents.
2.	Immunizations	Active immunization	Vaccinating healthy individuals to develop active immunity against the infection. With no consideration given to their safety profile, only a few vaccine candidates have shown demonstrable efficacy in eliciting adequate immune responses against CHIKV.
3.	Patient care	Host control	Infected patients are sources of the virus. Protecting the infected patient from further mosquito bites reduces the chances of transmission.
4.	Health education	Public awareness	Educating the public on the preventive strategies and how to seek medical care if they suspect they are infected. Moreover, describing the mosquito, its physical features and behavior.

Table 2.
Strategies for the prevention of spread of CHIKV.

3.3 Special care for the diseased

Just as the mosquito plays a major role in the transmission cycle of CHIKV, so does the infected patient. The already diseased patient is actually incubating the causative agent. It is, for this very reason, important that infected persons be protected from further mosquito exposure during the first few days of the illness when the viral load is high, so they can not contribute to the transmission cycle. Preventing further mosquito bites can be achieved through the same measures listed under the vector control and bite prevention strategies.

The main preventive strategies that could be adopted to limit outbreaks of CHIKV are briefly described in **Table 2**.

The world has not gone too far in developing a specific cure for Chikungunya fever. Apart from the common notion that 'prevention is better than cure', in the case of Chikungunya, prevention becomes of a particular interest because, until today, there are no specific antiviral therapies or vaccines (whether active or passive immunizations) that are proven to be safe and effective. It is hence important that centers of disease control and prevention pay due attention in this regard and take proactive measures to prevent or at least limit outbreaks.

4. Prospects on the introduction of new drugs and vaccines

As is the case with many other bacterial, viral or fungal infectious diseases, Chikungunya fever has been a subject of interest for many researchers in pursuit of new drug therapies and vaccines. Despite the fact that much effort has been done so far, there is still no antiviral proven to be specifically effective against CHIKV while being safe for use in humans [10]. Moreover, no vaccine has been made available

for use by humans. It is however worth reflecting the trends on the development of newer drugs and vaccines for chikungunya and to explore the various strategies employed in their development. This particular section summarizes the prospects in drug and vaccine development for Chikungunya fever.

4.1 Development of antiviral agents and the strategies employed

An antiviral agent is an entity that specifically targets a virus resulting in disruption of viral particles, prevention of replication and/or acceleration of viral clearance through immunological mechanisms.

There have been a number of trails conducted in pursuit of a safe and effective antiviral agents working specifically against the CHIKV. The candidates being tested in the different trials are variable and target CHIKV through variable ways. Some of the agents under study are small CHIKV inhibitor molecules and others are natural inhibitors of viral replication [8, 11]. There are also repurposed drugs, monoclonal antibodies, gene silencers and viral particles that work more or less through immune modulation. In the last decade, more than 30 antiviral agents that are thought to be effective against CHIKV were patented [8]. There are several antiviral agents studied so far, the description of some of which is briefly explored below.

4.1.1 Inhibitors of CHIKV

The CHIKV inhibitors is a category comprising a large array of compounds including small inhibitor molecules, inhibitors from natural sources, repurposed drugs and so on. This drugs utilize various biochemical pathways to inhibit the replication of CHIKV. There are several tens of agents being studied under this category, the majority of which are in the early stages of drug development. For instance, ribavirin, arbidol, chloroquine, Epigallocatechin Gallate (EGCG) and ribostamycin sulfate are some of the many drugs that fall under this category [8].

CHIKV inhibitors exert their antiviral actions through a number of mechanisms. Majority of these agents are viral replication inhibitors. They interfere in various stages of viral replication such as gene transcription, assembly of viral particles into virions and budding of virions out from the host cell. Other agents are thought to contribute to viral clearance by the immune responses. None of these agents has fully gone through the entire drug development process and thus non are made available in the market.

4.1.2 Monoclonal antibodies

The use of monoclonal antibodies in the treatment of various infectious and non-infectious diseases has been a very helpful strategy in the past few decades. Monoclonal antibodies are more or less a simple model of passive immunizations where preformed antibodies work to directly infiltrate viral particles.

There are many trials made on agents being developed as monoclonal antibodies to work against CHIKV. The introduction of antibodies that are effective against proteins of CHIKV could be a potential approach leading to vaccine development as a treatment. These agents that make use of the immune system of the host stimulates various immune modulators such as type I interferons and antibodies during the initial stages of an infection with CHIKV [12], Immunoglobulin M (IgM) antibodies during an acute phase [13] and Immunoglobulin G (IgG) antibodies for infections persisting longer [14]. Neutralizing antibodies can be of help to prevent budding of CHIKV from infected host cells and thus interfere with the viral release from the host stage of the replication process [15].

In this prospect, the use of Monoclonal antibodies seems to be a very promising approach towards the introduction of new antiviral treatments against Chikungunya in the not too far future.

4.1.3 Vaccines

Although generally and in principle vaccines have a bigger role in the prevention of acquiring active diseases, their use as therapeutic agents have become a commonly employed strategy especially in the essence of passive immunization where recipients are given readily made antibodies that directly work to neutralize the causative agent. The previously discussed principle about monoclonal antibodies was more or less preceded by such ideas about neutralization.

In the area of vaccine development against Chikungunya, various efforts have been made in the last decade to develop effective vaccines for the treatment of CHIKV infections. A number of live-attenuated virus vaccines, inactivated virus vaccine, recombinant viral component vaccines, DNA and mRNA-based vaccines, synthetic vaccines, subunit formulations of CHIKV and others have been developed [16]. Further details on vaccine development will be discussed in the section that follows.

4.2 Development of vaccines and the strategies employed

The introduction of vaccinations against CHIKV has been a subject of interest ever since the disease was first described decades back. Immunizations in general can be active and/or passive. Active immunization refers to the exposure of the body to a foreign entity resulting in the initiation of body's immune responses weather cell mediated or antibody mediated. The development of immunological memory will then result in prompt immune responses in subsequent invasions by the foreign agent to which memory was developed. On the other hand, passive immunization refers to the transfer, into the body, of readily made antibodies that may directly act upon the foreign entity in the body. In this case, the neutralization of the invading agent is much faster as there is no time lapse between sensitization and secretion of antibodies. In the development of vaccines against chikungunya, both types of vaccine agents have been under study [17].

4.2.1 Passive immunization

Passive immunization against the CHIKV refers to the introduction of preformed antibodies that directly act upon the causative virus. This is briefly discussed in the previous section where monoclonal antibodies are presented as therapeutic antiviral agents. Human protection from CHIKV infection is primarily mediated by humoral memory host response and the presence of neutralizing antibodies targeting the virus's outer surfaces of envelope glycoproteins [18]. There are studies that support the efficacy of monoclonal antibodies as post exposure therapy against CHIKV infections. Passive immunization therefore seems to be another prospect for the introduction of effective interventions against chikungunya in the future.

4.2.2 Active immunization

Active immunization employs the introduction of an antigen into the body to elicit an immune response and memory against the foreign agent. It is considered to be the most cost-effective preventive health intervention so far. The development of

Entity	Category	Description
Antiviral agent	Inhibitors of CHIKV (simple molecules)	• A group of compounds that interfere with various steps in the viral replication cycle. • More than 30 candidates under study. • Example: ribavirin and arbidol.
	Monoclonal antibodies	• Target specific immune modulators that neutralize virions. • Example: monoclonal antibodies that stimulate immune response mediators such as type I interferons, IgM and IgG in various stages of the infection.
Vaccine	Passive immunization	• Preformed antibodies that directly act to clear virions. • Fast onset of action (neutralization). • Example: serum purified antibodies.
	Active immunization	• Antigen based antibodies that stimulate the immune system to develop memory against CHIKV. • Example: vaccine candidates under development such as VRC-CHKV133, MVCHIK127 and CHIKV/IRES115.

Table 3.
CHIKV drug and vaccine development strategies.

a CHIKV vaccine seems to be feasible because the virus has a relatively low antigen diversity compared to other similar viruses [17]. This would also imply that changes in vaccine effectiveness profiles, assuming an effective vaccine is made available, are less likely to occur due to the less rapid rate of mutations observed with the virus.

Until 2016, three experimental vaccines have advanced to the stage of human testing. Two candidates namely, the VRC-CHKV133 and the MVCHIK127 vaccines finished phase I, in 2014 and 2015 respectively. The third candidate (CHIKV/IRES115 vaccine) yielded promising efficacy and safety results in mice and macaques and plans are in place for a phase I trial. It is worth of note that there is one candidate that have advanced to phase three trials in 2020 [9]. This prospect gave hope to many disease control program managers.

Table 3 provides a summary list of the most advancing drug and vaccine development approaches for CHIKV.

5. Chapter summary

Chikungunya fever is a vector borne infection caused by Chikungunya virus. The virus is transmitted by the bites of two main mosquito species namely, *Aedes aegypti* and *Aedes albopictus*. The disease is characterized by several symptoms the major of which are high grade fever, joint pain and joint inflammation. Severe infections are debilitating and may require the patient to be bedbound or may even result in death, though very rare, in cases where the patient has a compromised overall health status.

Currently, there are no specific anti-viral drugs against the Chikungunya virus and treatments are designed to alleviate symptoms. There are a number of palliative pharmacological and non-pharmacological treatment options which may offer symptomatic relief and accelerate recovery from the infection. The use of non-steroidal anti-inflammatory agents to alleviate fever, pain and various joint symptoms associated with the disease has been a very effective management option. Some other non-medicinal life style approaches like dietary changes such as consumption

of more vitamins and minerals to boost the immune response to the infection have also been some of the recommended care approaches. The overall goal of palliative care is to reduce suffering and accelerate recovery.

Exploring the various preventive strategies adopted to minimize the transmission of Chikungunya virus is of utmost importance. The general notion of disease prevention is more pronounced when treatment options are limited or inexistent. The absence of specific treatment for Chikungunya therefore necessitates that due attention is given to prevention. Although several strategies may be employed to prevent viral transmission, vector control has been the one major approach to halt spread of the infection. Prevention of mosquito bites becomes as important to the already infected as it is for the uninfected person in terminating the transmission cycle. In another scene, despite the recognition that immunizations have for so long been the most cost effective preventive health interventions and the efforts made to discover some, no specific CHIKV vaccine has so far been made commercially available and thus the use of vaccines as preventive measures is yet to come.

As it is the case with many novel viral diseases, Chikungunya has for decades been a subject of interest to drug and vaccine development firms. The current status and prospective with regard to new drug and vaccine development and clinical trials for cures and immunizations against this viral disease seems to be promising. Many new trails on animal models are currently underway and a few drug and vaccine candidates made it to testing in humans. Several tens of antiviral agents have advanced to the late stages of drug development. These entities come in various forms ranging from simple molecules, agents from natural sources and macromolecules such as monoclonal antibodies. On the other hand, a number of vaccines have also been under development and one candidate has so far advanced to phase three clinical trials, thus demonstrating acceptable safety and efficacy.

In light of the seriousness and debilitating nature of Chikungunya fever, the pursuit for newer treatment options and preventive strategies such as vaccinations should inevitably be encouraged. Neglected tropical diseases, as their name implies, have for long been ignored in many aspects in attempts to favor policies and resource allocations towards diseases that are deemed deserving priority based on their public health threat profile. Chikungunya fever is a neglected tropical disease, yet, the bulk of research carried out in this area is commendable and the trends demonstrate a possibility for the introduction of a novel treatment option in the near future.

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