

Therapeutic Approach for Chikungunya Infection

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Abstract

Chikungunya is endemic to sub-Saharan Africa and South and East Asia, in recent years, it has been expanding its horizon due to increasing international travel. Patients present with fever, headache, rash and severe symmetrical polyarthralgia. More than a million Chikungunya viral cases are reported annually, which can hamper individual's quality of life and most of the time they undergo long-term rheumatologic complaints. Despite the copious amount of extensive and prolonged research that has been conducted by researchers, an effective novel and potent anti-Chikungunya drug has yet to be developed. This review provides an overview on currently available treatments, and recent findings and progress in the development of major therapeutic strategies that are being evaluated as treatments for Chikungunya virus induced disease.

Keywords: Chikungunya; Infection

Introduction

Along with the likes of other ailments such as Herpes Simplex Virus (HSV), Ebola virus, and Human Immunodeficiency Virus (HIV), Chikungunya remains one of the numerous infections that is deemed to be generally incurable [1]. This convoluted disease was originally discovered and examined in the United Republic of Tanzania during 1952 [2]. Chikungunya virus is a mosquito transmitted (female *Aedes aegypti* and *albopictus*) alpha virus of the *Togaviridae* family. Although it is endemic to sub-Saharan Africa and South and East Asia, in recent years, it has been expanding its horizon due to increasing international travel [3,4]. In addition, globalization and climate changes are aiding the mosquitoes to spread to new geographic locations [5].

Chikungunya viral disease affects all age groups. After the typical incubation period of 4-7 days patients present with fever, headache, rash and severe symmetrical polyarthralgia [6,7]. Tarsal joints activities leads to extreme pain. Individuals with pre-existing underlying conditions, elderly and neonates are susceptible to Chikungunya viral disease with fatal outcome [8-10]. In terms of severity, Chikungunya is one of the milder and less harmful virus-associated ailments (compared to other viral-associated diseases, such as HSV or HIV) that most affected individuals are generally able to overcome without a significant degree of difficulty [2]. Even with the lack of an established medical product that could be used as a means to treat and cure the Chikungunya disease, the probability of a fatality resulting from such a trifling illness is generally low in the majority of cases [1].

More than a million Chikungunya viral cases are reported annually, which can hamper individual's quality of life and most of the time they undergo long-term rheumatologic complaints [11]. Despite the copious amount of extensive and prolonged research that has been conducted by researchers, an effective novel and potent anti-Chikungunya drug has yet to be developed [2]. The cases are spreading beyond endemic areas due to poor vector controls, elevating global temperatures and a lack of licensed vaccines or therapeutics. This review provides an overview on recent findings and progress in the development of major therapeutic strategies that are being evaluated as treatments for Chikungunya virus induced disease.

Current Treatments

Non-steroid anti-inflammatory drugs (NSAIDs), are the drug of choice for management of arthritis/arthralgia in addition to fluid intake to prevent dehydration. The other drugs such as aspirin may lead to bleeding and corticosteroids will cause immunosuppression. Disease-modifying anti-rheumatic drugs (DMARDs) such as sulfasalazine, methotrexate and hydroxychloroquine have been used in patients with chronic Chikungunya viral disease and those exhibit limited response to NSAIDs [12,13].

Treatment of Acute Chikungunya Disease

Treatment of acute Chikungunya virus disease can be broadly classified as virus-targeted (to reduce viral load) and host-targeted therapies (inhibit host cellular response or reduce host inflammatory response).

Virus-targeted antivirals

Ribavirin, one of the earliest broad-spectrum candidate antivirals in combination with interferon-alpha (IFN- α), which received FDA approval for the treatment of chronic hepatitis C virus and respiratory syncytial virus in infants, has been shown to reduce Chikungunya virus replication both *in vitro* and in a small clinical study [14-17]. Ribavirin is a synthetic guanosine nucleoside analogue that can inhibit the cellular inosine monophosphate dehydrogenase enzyme leading to depletion of cellular pools of GTP [18]. Mycophenolic acid has similar molecular mechanism as that of ribavirin and *in vitro* studies have shown anti-Chikungunya virus activity [19]. It is being used as an immunosuppressant in organ transplantations.

Other antiviral agents like Favipiravir (T-705 and with its de-fluorinated analogue T-1105) and Arbidol approved in Japan, Russia and China for the treatment against

influenza virus inhibited Chikungunya virus replication *in vitro* [20-22]. Similar broad-spectrum drug suramin (licensed for treatment against trypanosomiasis) have shown anti-Chikungunya virus effect *in vitro* [23]. The efficacy of these drugs needs to be verified using *in vivo* models of Chikungunya virus infection.

Harringtonine (a plant alkaloid compound) and its methylated derivative homoharringtonine (omacetaxine mepesuccinate), have shown anti-Chikungunya replication *in vitro* [24]. This compound is believed to compete with tRNAs and stop translation. In addition it can halt the synthesis of viral structural E2 protein and non-structural protein nsP3. This drug is being used for the treatment of chronic myelogenous leukemia [24-26].

An antimetabolite, 6-azauridine, which reduces the UTP levels and inhibit the replication of several DNA and RNA viruses has shown anti-*in vitro* Chikungunya virus activity. 6-azauridine (a uridine nucleoside analogue) inhibits the enzyme orotidine monophosphate decarboxylase leading to reduced level of pyrimidine [16,28,29].

Similarly, β -D-N4-hydroxycytidine (NHC- nucleoside analogue), was found to selectively inhibit Chikungunya virus replication *in vitro*. It has been previously shown to inhibit hepatitis C virus replication [30]. A number of novel antiviral agents have been found to selectively target nsP1 and nsP2, leading to inhibition of *in vitro* Chikungunya virus replication [31-33].

Several broad-spectrum antiviral compounds have passed clinical trials in humans for other conditions and have been shown anti-Chikungunya virus *in vitro* activity. Further future *in vivo* research is warranted before considering their use in a clinical setting and makes them available during Chikungunya virus epidemic.

Antibody therapies

Neutralizing antibodies have shown promising results as a prophylactic and therapeutic treatment strategy in animal models of Chikungunya virus infection [34,35]. Human convalescent-phase plasma passive transfer to neonatal and IFNAR-/- (IFN receptor knockout mice) has protected against Chikungunya virus disease [35]. A similar result has been illustrated with nonhuman primate polyclonal antibodies [34]. Moreover *in vitro* and mice model studies have shown viral neutralization by human and murine monoclonal antibodies (mAbs). These mAbs may be either combinatorial-mAbs or mAbs directed at the E1 and E2 domains [36-41].

Additionally, anti-Chikungunya virus mAbs used as prophylactic treatment for RAG1^{-/-} mice reduced viral titers in muscle tissue and sera [42]. Similarly, rapid viral clearance and low joint inflammation was observed in infected rhesus macaques after treatment with mAb-SVIR001 [43].

The above said mAb and polyclonal antibodies have shown promising results in the early phase of infection and can be used in humans at higher risk. However, Chikungunya virus-infected patients usually present several days after the onset of symptoms. To overcome the inflammatory process in such condition a combination therapy with 4N12 mAb and abatacept (T-cell costimulator inhibitor) was found to be very effective [44].

Anti-Chikungunya virus antibody therapies could be recommended for high risk populations, such as Chikungunya virus infected pregnant women during the late stage of pregnancy, to protect the child from Chikungunya virus induced neurologic disease, Anti-Chikungunya virus antibody might be administered to immunosuppressed individuals, known virus exposed laboratory personal or patients with known underlying conditions like cardiac failure, diabetes mellitus, and chronic obstructive pulmonary disease [44-47].

Prophylactic approaches would be recommended for patients living in Chikungunya virus-endemic regions. However, due to high costs for booster dose and logistical concerns about antibody delivery, its role during Chikungunya virus outbreaks remains unclear. Additionally these antibodies have short serum half-life, hypersensitive and high production costs. Future research is warranted to produce long term protecting, cost-effective and easily accessible antibodies.

Host-Targeted Antivirals

In vitro studies have shown that Chloroquine (antimalarial drug) prevents the entry of Chikungunya virus inside the cell by increasing the endosomal pH [48]. However, contrasting results have been obtained from *in vitro* and clinical trials. Human clinical trials have shown ineffective and even exaggerated arthralgia [49,50]. As host inflammatory response is the major key factor for the Chikungunya virus induced arthritides, researchers have tried host inflammatory response inhibitors such as Bindarit, as a treatment alternative. However, similar to Chloroquine conflicting results have been shown in

different rodent model studies. Future studies are warranted with nonhuman primate models of Chikungunya virus infection [51-54].

Therapies for Chronic Chikungunya Disease

Most of the patients suffer from chronic arthralgia even after years of post-infection. The pathogenesis of chronic Chikungunya virus-associated arthralgia is poorly understood compared to acute Chikungunya virus infection. Currently treatment options are NSAIDs and antirheumatic drugs (methotrexate) [13,39]. There is lot of lacunae in better understanding of host factors and the virus in chronic disease pathogenesis [13,39].

Other therapeutic approaches

In vitro and animal model studies have also used short hairpin or small interfering RNA elements as a therapeutic approach to restrict viral replication [54,55]. However, as this approach is entirely dependent on Chikungunya virus strains, viral mutation can significantly reduce the effectiveness. In future these limitations can be overcome by using multiple interfering elements.

Future Directions

Till date precise cellular mechanism of Chikungunya virus infection is not known. Although we know about the structure of virus and its role in pathogenesis, we know less about human target cell receptors [56,57]. Even though we know about the acute state of disease, chronic disease mechanism is yet to be delineated. Majority of Chikungunya virus pathogenesis studies have focused on *in vitro* and animal models. Currently 3D scaffolds and models of the GI tract, brain, kidney, lung, liver, and skin have shown promising results in studying infectious disease, as it is composed of multiple cell types established in a particular organ [58]. Similarly, 3D models can be utilized for understanding the molecular level pathogenesis in potential target organ systems such as brain, bone, cartilage, joints.

Conclusion

In conclusion, this updated mini-review summarizes the currently available treatment, current status of research progress and future directions for development of safe, affordable and effective therapeutics for Chikungunya virus infection.

Therapeutic Agents	Used for the Treatment of	Experimental Models used to Study Chikungunya Virus	Mechanism of Action
Current Treatment			
Non-steroid anti-inflammatory drugs (NSAID)	Acute arthritis/arthralgia	-	Inhibit the activity of cyclooxygenase enzymes (COX-1 and/or COX-2) leading to reduced prostaglandins
Fluid intake	Acute arthritis/arthralgia	-	-
Disease-modifying anti-rheumatic drugs (DMARDS's)	Chronic Chikungunya viral disease	-	Several
A. Treatment of Acute Chikungunya Virus Disease			
A1. Virus-Targeted Antivirals			
Ribavirin + IFN- α	Chronic hepatitis C virus and respiratory syncytial virus	<i>in vitro</i> and in a small clinical study	Inhibit the cellular inosine monophosphate dehydrogenase enzyme leading to depletion of cellular pools of GTP
Favipiravir (T-705 and with its de-fluorinated analogue T-1105)	Influenza virus used in Japan	<i>in vitro</i>	Inhibition of viral RNA-dependent RNA polymerase
Arbidol	Influenza virus used in Russia and China	<i>in vitro</i>	Prevents contact between the virus and target host cells
Suramin	Treatment against trypanosomiasis	<i>in vitro</i>	Combines glycolytic enzymes to inhibit energy metabolism
Mycophenolic acid	Immunosuppressant in organ transplantations	<i>in vitro</i>	Similar to ribavirin
Harringtonine and homoharringtonine (omacetaxine mepesuccinate)	Chronic myelogenous leukemia	<i>in vitro</i>	Compete with tRNAs and stop translation. halt the synthesis of viral structural E2 protein and non-structural protein nsP3
6-azauridine	An antimetabolite	<i>in vitro</i>	Reduces the UTP levels and inhibit the replication of several DNA and RNA viruses. Inhibits the enzyme orotidine monophosphate decarboxylase leading to reduced level of pyrimidine
β -D-N4-hydroxycytidine	Inhibit hepatitis C virus replication	<i>in vitro</i>	NHC- nucleoside analogue
Antibody Therapies			
Human convalescent-phase plasma	-	Neonatal and IFNAR $^{-/-}$ (IFN receptor knockout mice)	-
Nonhuman primate polyclonal antibodies	-	Neonatal and IFNAR $^{-/-}$ mice	-
Human and murine monoclonal antibodies (mAbs).	-	<i>in vitro</i> and mice model	-

Combinatorial-mAb or mAbs directed at the E1 and E2 domains			
Anti-Chikungunya virus mAbs used as prophylactic treatment	-	RAG1 ^{-/-} mice	-
mAb- SVIR001	-	Rhesus macaques	-
Combination therapy with 4N12 mAb and abatacept (T-cell co-stimulator inhibitor)	Chronic Chikungunya viral disease	-	-
A2. Host-Targeted Antivirals			
Chloroquine (contrasting results have been obtained from <i>in vitro</i> and clinical trials)	Antimalarial drug	<i>In vitro</i> and human clinical trials	Increasing the endosomal pH
Bindarit (conflicting results)	Host inflammatory response inhibitors	Rodent model studies	Inhibition of NFκB pathway
B. Therapies for Chronic Chikungunya Virus Disease			
NSAIDs and antirheumatic drugs (methotrexate)	-	-	-
Others			
Short hairpin or small interfering RNA elements	-	<i>In vitro</i> and animal models	-

Table: Therapeutic approach for Chikungunya infection.

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