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REVIEW

Development and Application of Treatment for Chikungunya Fever

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Abstract: The development and application of treatment for Chikungunya fever (CHIKF) remains complicated as there is no current standard treatment and many barriers to research exist. Chikungunya virus (CHIKV) causes serious global health implications due to its socioeconomic impact and high morbidity rates. In research, treatment through natural and pharmaceutical techniques is being evaluated for their efficacy and effectiveness. Natural treatment options, such as homeopathy and physiotherapy, give patients a variety of options for how to best manage acute and chronic symptoms. Some of the most used pharmaceutical therapies for CHIKV include non-steroidal anti-inflammatory drugs (NSAIDS), methotrexate (MTX), chloroquine, and ribavirin. Currently, there is no commercially available vaccine for chikungunya, but vaccine development is crucial for this virus. Potential treatments need further research until they can become a standard part of treatment. The barriers to research for this complicated virus create challenges in the efficacy and equitability of its research. The rising need for increased research to fully understand chikungunya in order to develop more effective treatment options is vital in protecting endemic populations globally.

Keywords: CHIKV, arthritis, treatment, natural, pharmaceutical

Introduction

As the emerging disease Chikungunya virus (CHIKV) is causing serious global health implications due to its socioeconomic impact and high morbidity rates, treatment for CHIKV remains complex.[1–7] CHIKV is an arbovirus in the *Togaviridae* family and is characterized by the National Institute of Allergy and Infectious Diseases as a category B priority pathogen, which is the second highest priority of biological agents.[5,7,8] CHIKV is transmitted by the vectors *Aedes aegypti* and *Aedes albopictus* mosquitoes in tropical and subtropical regions, and in the last two decades, temperate regions.[1,5,7] Vertical transmission is also important and can result in neonatal mortality and abnormalities, since many different cell types are susceptible to CHIKV.[2,9–11] In terms of impact of the virus, CHIKV is estimated to be the cause of over 158,000 disability-adjusted life years (DALYS) lost every year in the Americas.[3] This is a significant negative impact, but the virus does not only affect this region as it has also been reported in Europe, Asia, Africa, and Australia.[10,12]

The ability of CHIKV to spread across the globe is a result of its variation in viral genetics.[3,13] It is reported that CHIKV first emerged in 1952 in Tanzania.[2,14,15] It remained isolated in this tropical/subtropical region due to the limited range of *Aedes aegypti* mosquitoes, which cannot survive in temperate regions.[2,14,15] It was not until the 2005 outbreak in La Reunion Islands when CHIKV showed the remarkable A226V mutation that gave it the ability to be transmitted by Aedes albopictus mosquitoes, which can survive in temperate regions, increasing its viral infectivity.[2,3] This mutation, along with increased propagation due to human driven activities, allowed for CHIKV to spread across the globe.[3,13,16] The appearance of CHIKV in temperate regions lead to densely populated and wealthy regions of the world experiencing the disease, like the outbreaks in Italy in 2007 and France in 2010.[4,17,18] Regardless, CHIKV continues to disproportionately affect low resource areas the most where healthcare and public health surveillance are limited.[10] Due to

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inconsistencies in diagnostic testing which likely leads to underreporting in these areas, it is impossible to know the full implications of the virus globally.[3,10,12,14,20]

Currently, treatment for CHIKV is focused on relieving symptoms and is complex as there is no current dedicated vaccine or treatment.[1,5–7,21] Acute infection has a 2–7-day incubation period, and about 95% of infected persons develop symptoms, which resolve in about two weeks.[5,7,19,23] During the acute stage, arthralgia is similar to dengue or zika virus, so serological detection is needed for definitive diagnosis before treatment can be administered.[3,29] CHIKV rarely leads to death, and when it does, it usually only occurs in the most vulnerable population of elderly individuals with comorbidities and children.[24,25] Common acute symptoms include fever, joint pain, joint swelling, muscle pain, headache, nausea, fatigue, and rash.[5,7] However, less common symptoms can occur including uveitis, retinitis, myocarditis, cardiomyopathy, hepatitis, nephritis, bullous skin lesions, hemorrhage, encephalitis, meningoencephalitis, myelitis, Guillain-Barré syndrome, cranial nerve palsies, synovitis, tenosynovitis, Raynaud's syndrome, or relapse of rheumatologic symptoms.[9,19,23–28]

Chronic symptoms of CHIKV include the development of a chronic or reoccurring form of CHIKV-associated arthralgia or arthritis, but this development is poorly understood, and a causal relationship has yet to be establish despite an estimated 40% of patients progressing with chronic pain and a compromised quality of life.[1,6,19,24,30] Causes of chronic CHIKV-associated arthralgia or arthritis have been suggested in evaluations of these cases and identified as viral persistence, induction of autoimmune disease, and exacerbation of pre-existing joint disease, even though only 2.8% of those who developed chronic arthralgia had pre-existing joint pain as reported after the La Reunion outbreak.[19,21,31,32] Severe chronic CHIKV-associated arthralgia or arthritis can last months to years, affecting a person's mobility and requiring life-long treatment.[2,5,19,24,33] Yet with no current standard treatment for, creating treatment plans can be complicated, especially due to the vast amounts of research on both natural and pharmaceutical treatments for the chronic symptoms of CHIKV.[1,5–7,21]

The demand for treatment and vaccine research for CHIKV remains elevated as the high rate of morbidity caused by the virus creates significant psychosocial and economic impacts which affect the health and well-being of individuals, populations, and the globe as a whole.[2,3] There is an urgent need for the development of alternative natural and pharmaceutical countermeasures to this emerging viral infection that can be used in low resource areas of the world where this virus affects the most.[1,10] This review will demonstrate the development and application of treatment for CHIKV in research and the barriers to researching this complicated virus.

Natural Treatments

In order to understand the types of natural treatments that are used for CHIKV, it is easiest to break them down into prevention, homeopathy, physiotherapy, and home remedies. Each of these treatments has a role in minimizing the impact of CHIKV in the endemic areas it affects. While pharmaceutical therapy is most often thought of first in western cultures for treatment options, this section will show that natural treatments have the ability to effectively benefit people with chronic CHIKV-associated arthralgia or arthritis.

Prevention

Integrated control of epidemiological surveillance and environmental management to eliminate mosquito breeding are important factors to reducing the transmission of CHIKV.[3] Preventive measures are the most effective protection for environmental management of mosquito vectors and include wearing long sleeves to minimize the amount of skin surface exposed to mosquito bites, using mosquito nets, elimination of mosquito breeding sites like standing water where mosquitoes could lay eggs, use of insecticides and the installation of window and door screens in homes.[1,5,7,19,23] However, total prevention of transmission from environmental management is impossible due to CHIKV misdiagnoses and underdiagnoses in many regions and its disproportionate effects in low resources areas.[1,3]

When preventative measures fail, a person's acute CHIKV symptoms are generally treated with fluids, rest, and pharmaceutical medications for pain management determined by a physician.[5,7] Antipyretics and analgesics are pharmaceutical drugs that have many contraindications and not everyone is able to use them for pain management, and they have many side effects that can occur from chronic use.[5,7] Therefore, natural treatment options, like homeopathy and

physiotherapy, are important when it comes to CHIKV treatment in order to give patients a variety of options for how to best manage their acute and chronic symptoms.[26]

Homeopathy

Homeopathy is the use of medical plants, herbal products and compounds from both natural and unnatural sources as treatment and prevention against diseases, which has been used for millennia in traditional medicine and is still widely practiced.[35] Plants can be used to protect people from diseases because they are persistently challenged by viruses to protect themselves and have developed multilayered surveillance against all pathogens.[36,37] Plants have become increasingly researched as potential sources of natural antiviral drugs that could be effective in treating the chronic symptoms of CHIKV.[36] With their ability to impede with viral replication, enhance the host immune response, improve symptoms, and reduce mortality with minimal toxicity, homeopathy is ideal for CHIKV treatment.[36,38,39]

The first study performed with homeopathic medication for chronic CHIKV-associated arthritis was by Wadhwani et al[40] in 2013. The homeopathic remedies used included: *Lycopodium*, radium bromide, *Arnica montana, Bryonia alba* followed by *Rhus toxicodendron, Rhus toxicodendron* followed by *Bryonia alba, Ignatia amara, Calcarea carbonica, Calcarea phosphorica, Lachesis muta, Natrum muriaticum*, and *Phytolacca decandra*.[40] As a result, 90% of the cases of chronic arthritis achieved cure after an average time of 32.5 days and no patients reported continuing conventional therapy.[40] Due to this, homeopathic prescription was viewed as an alternative to be further explored.[40]

Since then, the flora from the Mascarene Islands, which is comprised of Reunion, Mauritius, and Rodrigues Islands and is known as a biodiversity hotspot and have been studied for their wide therapeutic activity including antiviral properties.[36] Antiviral activity of ethyl acetate extracts of Mascarene plants against CHIKV was identified in *Doratoxylon apetalum, Aphloia theiformis, Indigofera ammoxylum, Croton maritianus, Securinega durissima, Ethyoxylum sideroxloides, Phyllanthus phillyreifolia*, and *Stillingia lineata* in cell culture studies.[41–45] However, *Stillingia lineata* was the most effective in cell culture against CHIKV and was reported as the most viable candidate for potential development of effective natural antiviral drugs.[36]

Other natural compounds in cell culture have been shown to demonstrate antiviral activity against CHIKV and could be useful in the treatment of acute and chronic symptoms.[34,38,46] Baicalein, the root of *Scutellaria baicalensis* and *Scutellaria lateriflora*, inhibits viral attachment to host cells and has potent virucidal activity against extracellular viral particles.[38,46,47] Curcumin, *Curcuma longa* (turmeric), also inhibits viral attachment to host cells.[38,46,48] *Epigallocatechin gallate* (EGCG), from the leaves of *Camellia sinensis* (green tea), possibly shows evidence of inhibiting viral attachment to host cells.[38,46,49] Fisetin, the pigment in various flowers and fruits, inhibits early stages of viral replication.[1,38,47] Harringtonine, *Cephalotaxus harringtonia*, possibly inhibits viral protein synthesis.[1,38,50] *Quercetagetin*, leaves of eriocaulon species, inhibits viral attachment to host cells and has a neutralizing effect against extracellular CHIKV particles.[38,46,47]

Plant extracts in cell culture can also show signs of antiviral activity against CHIKV.[36,38,46,51] *Silymarin complex* (Silybin) and seed of *Silybum marianum* (milk thistle), inhibit post-entry stages of viral replication cycle reducing CHIKV replication efficacy.[36,38,46,51] *Ipomoea aquatica* and *Persicaria odorata* inhibit the cytopathic effect of CHIKV.[46,52] *Rhapis excelsa, Tradescantia spathacea* and *Vernonia amygdalina* all have a direct virucidal effect.[46,52] *Andrographis paniculata* inhibits viral genome replication.[46,53] *Phyllanthus niruri* and *Tinospora cordifolia* inhibit virus entry.[46,53] *Oroxylum indicum, Cynodon dactylon* and *Psidium Guajava* all inhibit viral replication.[46,53] Aquatic plant extracts that inhibit viral replication include *Picrorhiza kurroa, Ocimum tenuiflorum, Terminalia chebula* and *Zingiber officinale* while *Commiphora wightii* and *Cedrus deodara* inhibit viral attachment.[46,54] Also, phytochemicals targeting CHIKV infection include andrographolides, nobiletin, flavaglines, and the phytochemicals of *Tectona grandis lin*.[46] Lastly, the polyherbal formulation, *Nilavembu kudineer*, shows promising antiviral activity against CHIKV.[46,55]

Additionally, polyphenols are naturally occurring compounds found in fruits, vegetables, wine and tea that have been widely researched in cell culture for use in pharmacology due to their antiviral, anti-bacterial, antioxidant, anti-inflammatory and anti-carcinogenic effects.[38,56] They are secondary metabolites of plants that are involved in protection from UV radiation, microbial infection, and defense against insects.[57] As natural plant extracts, they have the potential to

be included in the standard treatment for chronic CHIKV-associated arthralgia or arthritis with further research as they have minimal side effects.[38]

Scientific studies have shown the therapeutic effectiveness of homeopathy and its future potential effects against CHIKV.[46] While they have been shown to be effective in vitro, they have not been evaluated in vivo yet. Further studies for their therapeutic efficacy in animal models, safety profiles, and mechanisms of action at the molecular level may lead to finding a suitable remedy that can become a standard part of treatment.[38,46]

Physiotherapy

Physiotherapy is a therapeutic technique involving exercises to enhance mobility and quality of life that is used by professionals as treatment for injuries or other health conditions, like chronic CHIKV-associated arthralgia or arthritis.[25,58] Specific physiotherapy treatments have been used in clinical trials and show promise, with more research, they could become part of standardized treatment from chronic symptoms of the virus. A study performed by Neumann et al demonstrated that resistance exercises should be considered as a treatment approach for patients with musculoskeletal disorders from chronic CHIKV-associated arthralgia or arthritis, as it improved their overall physical functioning.[59] Oliveira et al utilized Pilates in a 12-week trial to examine whether patients would have less pain and better overall functioning, quality of life, and increased range of joint movement. They were able to show that Pilates is an effective treatment for patients with chronic CHIKV-associated arthralgia or arthritis.[60] Lastly, another form of physiotherapy being researched for treatment of chronic arthralgia and arthritis called transcutaneous electrical nerve stimulation (TENS).[6,30] TENS uses ultrasound and an infrared laser to increase blood flow, capillary permeability, muscle contraction, nerve conduction, and extensibility of collagen in specific parts of the body.[6,30] TENS can also release endorphins from stimulating the sensory fibers that block primary nociceptive fibers and reduce pain and produce photochemical reactions that activate cellular enzymes to increase cell proliferation, accelerating healing process.[6,30]

Physiotherapy is a useful tool for people with chronic CHIKV-associated arthralgia or arthritis to cope with the severe pain of the disease.[25,58] With increased research, physiotherapy practices can be better integrated into medical practice and become a part of standard treatment for chronic symptoms.[6,30,59,60] However, CHIKV symptoms may manifest differently in different people, so it is crucial to note that research in this field will always be advancing as it is essential to have a variety of treatment options so that patients can figure out what works best for them and their pain and lifestyle.[26]

Home Remedies

With the limitations of treatment for CHIKV and the high prevalence of it in low resource areas, home remedies have become popular in the media in various regions.[10] Common media suggestions for treatment include rest and fluids, which are backed by scientific research.[5,7,61–63] However, the home remedies presented in the media are not linked to any scientific studies but based upon folk remedies and traditional medicine such as Ayurveda.[61–63] Most home remedies from India are geared towards reducing pain, inflammation and fever.[61,63,64] One report recommended garlic paste with clove oil or sunflower seed soaked in honey applied on the skin, or even a hot water bath with Epsom salt in order to reduce pain and inflammation.[63] They also recommended the consumption of turmeric for its anti-inflammatory properties, carrots to improve immunity, Tulsi to reduce fevers, and coconut water to detoxify the body for faster recover.[63]

Another report recommended consuming Giloy, papaya leaves, and basil leaves to reduce fever, which are all similar to Tulsi.[64] Similar to the other report, they recommended coconut water and turmeric.[64] An additional home remedy they recommended to reduce pain and fever was grapes with cow's milk.[64] Lastly, they recommended olive oil and vitamin E for rashes.[64] Another report from India added the consumption of ginger or green tea to relieve inflammation, but most importantly they included low impact aerobic exercise and light massage to relieve chronic joint pain which is consistent with research for improving symptoms related to chronic CHIKV-associated arthralgia or arthritis.[25,58,61]

One media report focused on the types of home remedies being used to treat symptoms of CHIKV in the Caribbean.[62] They named naturopathy as the main type of homeopathic treatment.[62] Many of naturopaths in the region agree that a tea brewed of echinacea, chaparral, and burdock root drunk three times per day will purify the blood, ease pain, and soothe the rashes caused by CHIKV.[62] While homeopathy and naturopathy are not rooted in research or recommended by

medical doctors, these types of home remedies usually do not result in any harm.[62] However, many of these home remedy ideas presented to the public by the media, are not too different from the medical treatment recommendations when it comes to the thought processes behind them in focusing on treating the symptoms caused by CHIKV through rest, fluids, anti-inflammatories, fever reducers, pain reducers, and exercises for chronic joint pain.[5,7,25,58,61–64]

Pharmaceutical

Currently, there is no single recommended treatment therapy for CHIKV.[65] As a result, many drugs have been used with varying success. Many focus on supportive treatment and reducing joint pain.[62] Some of the most used pharmaceutical therapies for CHIKV include non-steroidal anti-inflammatory drugs (NSAIDS), disease-modifying antirheumatic drugs (DMARDs), and antivirals.

NSAIDS

Over the counter NSAIDs are often used to relieve mild arthralgia pain and reduce fever in CHIKV positive patients and are currently the most routinely used treatment.[66] A majority patients are reactive to NSAIDS, with about 89% of patients experiencing some immediate pain relief.[67] Although many physicians rely on NSAIDs as a means to control symptoms, they may provide limited pain relief and are recommended only in mild cases, usually a one to three on the visual analog scale (VAS) for pain.[68] There is no conclusive evidence that beyond moderate NSAID treatment in more severe cases show any efficacy.[19]

Although NSAIDs are often used in CHIKV symptomatic patients, it should not be given until dengue is ruled out as the possible cause due to an increased risk of internal bleeding in dengue patients.[5] In these instances, acetaminophen or paracetamol can be used.[5] Before use of NSAIDs, comorbidities such as liver disease and heart failure should be evaluated as some may contraindicate its use.[68] Even with its limitations, NSAIDs are used due to the relief it gives in nearly all patients and its worldwide availability.[69]

DMARDS

Methotrexate

Another drug used for CHIKV is MTX. MTX serves as the foundation of most rheumatic arthritis (RA) treatments due to its anti-inflammatory properties.[70–72] These properties come from inhibition of proinflammatory cytokines interleukin (IL) 1, IL-6, IL-8, and tumor necrosis factor alpha (TNFa) which have been found to be correlated with disease severity in both RA and CHIKV-related arthralgia.[65,73] Javelle et al have exhibited MTX to reduce pain scores in 80% of patients studied by a minimum of two points on the pain VAS, a ten-point scale, after four weeks of treatment.[69] However, pain relief seems to plateau after the four-week mark.[69] Additionally, patients have found reduction in joint swelling with an average reduction from 7.15 to 2.89 after four weeks in those with frank arthritis.[65] MTX can be prescribed to patients for months or even years post CHIKV infection.[74]

MTX can be given as part of a monotherapy or multidrug therapy.[65] In clinical trials, MTX monotherapy has demonstrated its effectiveness in reducing arthralgia pain, but pain reduction was significantly higher in combination therapy groups.[75] Combination therapy with MTX is most often paired with hydroxychloroquine.[75] Together, patients show a larger decrease of pain using VAS pain scores.[75] In addition, there is a reduction in pain edema and tendon improvement in patients.[6,75] There is a need for more randomized placebo trials for MTX monotherapy for chikungunya-related arthritis pain for further study.

Chloroquine

Chloroquine and hydroxychloroquine are drugs that are used for Malaria patients in endemic countries that have also exhibited to inhibit in vitro viral replication for human immunodeficiency virus (HIV) and alphaviruses.[69,76] In cell cultures, chloroquine and hydroxychloroquine have been shown to have dose-dependent antiviral properties against the chikungunya virus.[66,69,77] However, when used on patients, the drugs showed no beneficial effects.[66,69] The drug did not impact viremia and viral load in the patient, but did affect IL-6 and IFNa as time progressed.[78] Chloroquine in the acute phase can decrease cytokine levels, delaying the adaptive immune response in the patient.[78] When added as a part of

combination therapy with NSAIDs and corticosteroids, chloroquine offered no additional benefits besides NSAID monotherapy.[79] Still, the drug is implemented to treat CHIKV; possibly because it is available in countries where CHIKV outbreaks occur as shown in the 2005–2006 outbreak in Reunion Island, as it was noted that there was an increase in chloroquine usage.[78]

Sulfasalazine

Sulfasalazine, alternatively known as 5-aminosalicylic acid and sulphapyridine, is employed in treatment for inflammatory diseases such as RA and Crohn's disease.[80,81] Its mechanism of action is inhibiting nuclear factor-kappa B cells and TNFa which are both associated with inflammatory processes within the body.[80–82] In CHIKV viremic mice, those treated with sulfasalazine showed less inflammation and less tissue damage ten days post infection than untreated mice.[82] Although monotherapy has shown to lessen the severity of disease, sulfasalazine is often used in combination with ribavirin and hydroxychloroquine.[73,81,83] When used together, there is a significant reduction in pain and disability.[73] There are no studies directly comparing sulfasalazine monotherapy and combination therapy.[84]

Antivirals

Ribavirin

Ribavirin is an antiviral that is being researched for therapeutic benefits in CHIKV patients.[6] However, the mechanism of action is not currently known.[6] Ribavirin is a broad-spectrum antiviral that is used for patients with influenza, hepatitis C, and polio.[85] When used in ICR mice, ribavirin has shown a reduction in chikungunya viral load and joint inflammation along with inhibition of CHIKV replication.[86] With ribavirin as their treatment, patients with polyarthritis from a chikungunya infection reported improvement, claiming a reduction in pain and joint swelling.[87] Patients expressed an increase of progress with walking (70% in patients vs 30% in the placebo group) along with a reduction of edema (80% vs 60%).[87] However, the dose at which ribavirin is needed to be effective in human patients is highly associated with side effects including pulmonary and hematologic complications.[88]

6-Azauridine

6-Azauridine is a broad-spectrum antimetabolite used to combat RNA and DNA viruses.[76,77,89] When compared to ribavirin, 6-azauridine has proven to be more effective against CHIKV even when used at low concentrations.[70,89,90] 6-Azauridine inhibits DNA and RNA viral replication via inhibiting orotidine monophosphate decarboxylase enzyme, an enzyme used in the synthesis of pyrimidines.[76] In in vivo studies, the antiviral properties are not as effective as in in vitro showing a need for more research into the drug.[77]

Arbidol

Arbidol is a broad-spectrum antiviral drug used as prophylaxis and treatment for respiratory infections such as influenza in Russia and China.[76] In vitro studies with MRC-5 cells, arbidol has shown to inhibit CHIKV infection with limited knowledge of its mechanism of action.[77,91] It is theorized that the anti-CHIKV properties arise from inhibition of the viral life cycle in its early stages.[92] A mutated strain of CHIKV showed resistance to arbidol which stemmed from a mutation in the A portion of the E2 glycoprotein with glycine mutating into arginine.[70,77,92] The E2 envelope protein helps facilitate binding to host receptors.[93] This mutation suggests arbidol prevents entry of CHIKV into host cells, possibly preventing infection in the individual.[77] In vivo applications are unknown as no animal studies on the drug and CHIKV have been completed.[91]

Biologics

Immunoglobulins

Since treatment for the chronic symptoms caused by CHIKV continues to result in a high burden of morbidity for many populations, more effective treatment options are essential.[1–7] One potential therapy for CHIKV patients is immunoglobulin therapy. The goal for this type of therapy is to control the proinflammatory reaction of the virus in macrophages using intravenous Flebogamma.[94] Flebogamma is a product of thousands of donors, and thus has antibodies to a large amount of different pathogens.[94] Immunoglobulin therapy has four mechanisms that occur.[94] The first one is a reduction

of IL-3, IL-4, and IL-5 that are a part of the body's proinflammatory response.[94] Secondly, it affects the Fc receptors that inhibit phagocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC) that contributes to cell death, and antibody production.[94] Thirdly, the antibodies binding to the Fc receptors interrupt MAC formation, a part of the adaptive immunity that targets cells and causes apoptosis.[94] Lastly, the therapy causes cell death via FcR independent and dependent mechanisms.[94] Immunoglobulin therapy be utilized as prophylaxis where it has shown the antibodies prevented a CHIKV infection.[30] When immunoglobulin therapy is used in a viremic patient, the dose is tissue-specific, but effective in both adults and neonates.[32,95] More research would be needed on the efficacy of the treatment.[32]

Fingolimod

Fingolimod (FTY720) is an FDA-approved immunomodulating drug and sphingosine-1-phosphate receptor agonist that is primarily used for treating multiple sclerosis.[96–99] This receptor is responsible for releasing T-lymphocytes into the lymph nodes.[99] Inhibition prevents the T-lymphocytes, specifically CD4+ T lymphocytes, from reaching infection sites where edema and joint swelling will result in a CHIKV infected patient.[97,99,100] A study using C57BL/6 mice showed inhibition of CHIKV-specific CD4+ T lymphocytes entering joints that the virus has already infected, reducing joint swelling while not decreasing the viral load.[100] Fingolimod shows potential for both prophylactic and therapeutic treatment for CHIKV.[96,100] There has been no research done on the efficacy of the drug in CHIKV positive humans.[93]

Abatacept

Another treatment for chikungunya is abatacept, which is a modified human IgG protein that was approved by the FDA to treat RA.[83] Miner et al showed that abatacept suppresses T-lymphocytes stimulation and accumulation in affected joints when administered in CHIKV positive mice.[83,101–103] While the drug reduced joint swelling severity as mono-therapy, when combined with human anti-CHIKV monoclonal antibodies, there was a decline in pro-inflammatory cytokines, chemokines, and infiltrating leukocytes.[83,103] More research needs to be done to further explore abatacept and its anti-CHIKV properties.

Vaccines

Currently, there is no commercially available vaccine for CHIKV.[66] Even though active immunization is the most cost-effective prevention method, lack of funding has proven one of the leading barriers for the lack of an effective CHIKV vaccine.[86] In the early 1960s, the United States Army Medical Research Institute with an isolated strain from Thailand.[66] In 1971, the vaccine was brought to trials, being tested in two cohorts of eight.[86] It produced a 100% seroconversion rate two weeks after a second dose, but the vaccine was never completed due to lack of funding and interest from United States investors.[66,86] Around the same time, another vaccine was produced using attenuated strains, but failed due to the vaccine's ineffectiveness.[66] Another vaccine was created with the La Reunion isolate.[66] This isolated strain created large amounts of neutralizing antibodies when introduced in mice with future protection against CHIKV and cross-protection against o'nyong-nyong virus.[66] The types of vaccines that have been created to prevent chikungunya include live-attenuated vaccines, DNA-based vaccines, adenovirus-based vaccines, poxvirus-based vaccines, mRNA vaccines, and inactivated virus-like particles (VLPs).[86,104]

Although there have been several attempts at a CHIKV vaccine over the past few decades, only three have reached human testing.[86] The VRC-CHIKVLP059-VP, or VRC-CHKV vaccine is a vaccine from virus-like particles with envelope proteins from a chikungunya

Africa and created by Lee-Jah Chang et al.[86] In the clinical trial, no participants experienced arthralgia, but 40% experienced malaise, nausea, headaches, and mild injection site tenderness.[86] The vaccine showed to have a 100% seroconversion rate with a one-month titer level after a third dose is similar to that of those after a natural chikungunya infection.[86] A second vaccine to go to human testing is a vaccine using live attenuated measles virus (MV) as a base using surface proteins from a strain from La Reunion.[86] The MV-CHIK vaccine increased neutralizing antibodies with a 100% seroconversion after the second dose.[86] However, the antibody titers cannot be directly compared to that of a natural infection due to assay differences.[86] The third is a single dose live attenuated vaccine using the La Reunion strain.[22] Healthy volunteers had a 100% seroconversion rate after two weeks of administration, which was sustained for

one year.[22] Even though multiple drugs have made it to clinical trials with promise, funding is an issue that limits the research made for safe, effective vaccines against chikungunya.[86]

Barriers to Research

CHIKV is considered a neglected tropical disease, which means it does not get priority in funding for research and public health outreach programs.[105] This lack of funding has created a large obstacle for vaccine and therapeutic therapies.[105] Vaccine studies have been halted in the past due to lack of funds and interest in its completion.[63] This may be a result of lack of interest in wealthier countries where CHIKV is not endemic, as the disease is associated with impoverished areas of developing countries.[10,105] Wealthy countries such as the United States are wary to invest as CHIKV vaccine and therapy development as it has a limited economic demand and low market potential.[71] In addition, arboviruses get most attention during acute epidemics, but are rarely heeded in regards to ongoing endemic transmission.[76] This lack of interest and funding culminates in a severe deficit of life-saving studies that would impact millions globally.

Even when studies have sufficient support, many CHIKV cases go undiagnosed or unnoticed.[106] Many communities where the disease in endemic do not have laboratory equipment or adequate health-care services for recordings of diagnoses or CHIKV-related deaths.[106] As CHIKV, like other neglected tropical diseases, primarily affects the poor, infected individuals may not seek care due to high costs or treatment.[76] Those who are able to seek help are faced with language barriers or illiteracy, making informed consent for treatment and research difficult.[107] Affected areas are in need of an increase in resources and an increase in surveillance to allow for a more adequate account of incidence and prevalence.[10]

Conclusion

CHIKV mounts a serious global health problem, negatively affecting the socioeconomic status and health-care systems in countries across the world.[1] Although there is no current commercially available vaccine, current treatment is supportive with alleviating symptoms and relieving pain with a focus on fluids, rest, and physiotherapy.[63,66,71] Many current pharmacological and homeopathic treatments can also assist with alleviating symptoms, but treatments are complex and are not effective for everyone.[1,10] Barriers to research keep the treatment for the chronic symptoms related to CHIKV at a standstill until wealthier countries or companies begin to invest in the health of low resource populations.[1,10,38,46] Although research and treatment is complex, there is a rising need for research to fully understand CHIKV to best protect endemic populations globally that needs to be addressed.

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