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Review Article

Pain in Patients Infected by Chikungunya Virus

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Abstract

Background and Methods: The chikungunya virus has caused major epidemics around the world in recent years leading to significant morbidity. The epidemic crossed international borders as the virus was introduced in geographic regions where the vector is endemic. The disease has an acute phase that lasts about 10 days however many patients may develop subacute and chronic symptoms that can last for years causing pain with great suffering and disability.

Aim: The aim of this study was to review the literature on chikungunya fever and its clinical management with emphasis on pain symptoms presented by patients affected by the disease.

Contents: Describes the Chikungunya fever, the various outbreaks worldwide in recent years as well as the monitoring and management of patients.

Conclusions: The chronic joint pain presented by patients who were infected by chikungunya virus can be debilitating and disabling generating functional and economic impact on society. Studies are inconclusive about the cause and treatment to be implemented in these cases. Faced with the prospect of large increase in the number of infected patients in the coming years and consequently increase in cases of chronic joint pain, studies are required to elucidate these questions.

Keywords: *Chikungunya; Pain; Arthralgia; Fever; Alphavirus*

Introduction

The chikungunya virus (CHIKV) is an arbovirus of the alphavirus genus of the Togaviridae family [1]. It was first described in 1952 - 1953 during an epidemic in Tanzania. The name comes from a word in Makonde, a language spoken by Makonde people, who inhabit a region in southeastern Tanzania and northern Mozambique, which means "the one that bends" because of the position adopted by the patient due to intense joint pain. There are two known vectors of CHIKV, *Aedes aegypti* and *Aedes albopictus* with diurnal habits. Man serves as the primary reservoir during epidemic periods. Outside of this period, several other animals may be potential reservoirs such as other primates, birds and small mammals. After exposure to CHIKV, individuals develop immunity that will protect them from reinfection [1]. This article aims to compile the current knowledge of the disease known as chikungunya fever in view of the increased occurrence of this disease in Brazil and the difficulty faced in the treatment of chronic pain developed by many patients. The database used was Medline, EPub and Clinical Key using the words chikungunya, arthralgia and chronic pain indicators. The bibliographic research was also carried out on the official websites of the Brazil Ministry of Health and the World Health Organization. Due to the scarcity of available articles, there was no limitation on the period of publication of articles.

Reported Epidemics

Outbreaks initially occurred in small rural communities in Africa and Asia until reports began in urban communities in 1960 in Thailand and 1970 in India. After the initial identification of CHIKV, sporadic outbreaks continued to occur, but little activity was reported. In

2004, however, an outbreak originated on the Kenyan coast subsequently spread to Comoros, Reunion Island, and several other islands in the Indian Ocean in the following two years. The epidemic spread from the Indian Ocean to India where major outbreaks occurred in 2006. Infected travelers have taken outbreaks from India to the Andaman and Nicobar Islands, Sri Lanka, Maldives, Singapore, Malaysia, Indonesia. Also re-emerge in Reunion Island. In 2010, imported cases were also identified in Taiwan, France and the United States. In 2016, PAHO reported 349.936 suspected and 146.914 laboratory confirmed cases of Chikungunya fever. Brazil reported the great majority (265.000 suspected cases), but there were also reports in Bolivia and Colombia (19.000 suspected cases). Also in 2016 Argentina reported the first autochthonous transmission of chikungunya following an outbreak of more than 1.000 suspected cases. In the African region, Kenya reported an outbreak of chikungunya resulting in more than 1.700 suspected cases. In 2017, Pakistan continues to respond to an outbreak which started in 2016. CHIKV has the ability to emerge, re-emerge and spread rapidly in new areas [2]. Chikungunya fever is already a disease of mandatory reporting in Brazil but diagnostic tests are not widely available, probably leading to underreporting. According to Brazil Ministry of Health there were 271.824 suspected cases in 2016 with 196 fatal cases [3].

Clinical Condition

After an incubation period of 1 to 12 days from the infected mosquito bite, some patients develop symptoms. About 3% to 28% are asymptomatic. The acute phase lasts 3 to 10 days and is characterized mainly by high fever and intense joint pain. Other symptoms such as headache, back pain, myalgia, nausea, vomiting, skin rash and conjunctivitis may occur. The fever may be continuous or intermittent. Joint pain is usually symmetrical, more common in the hands and feet, and may involve proximal joints. There may be edema usually associated with tenosynovitis. About half of the patients may present maculopapular cutaneous rash on the trunk, face, palm of the hands and feet. Laboratory tests may reveal discrete thrombocytopenia, leukopenia, and altered liver function in addition to elevation of C-reactive protein [4].

Even in these acute phase, atypical manifestations may occur such as: neurological (meningoencephalitis, encephalopathy, seizure, Guillain Barre syndrome, cerebellar syndrome, paresis, paralysis, neuropathy), ocular (optic neuritis, iridocyclitis, episcleritis, retinitis, uveitis), cardiovascular (myocarditis, pericarditis, heart failure, arrhythmias, hemodynamic instability), dermatological (hyperpigmentation, vesicobolous dermatosis), renal (nephritis, acute renal failure), and others (blood dyscrasia, pneumonia, respiratory failure, hepatitis, pancreatitis, syndrome of inappropriate secretion of antidiuretic hormone) [5,6].

After the initial 10 days, patients improve their symptoms but, after 2 to 3 months, there may be a marked increase in joint symptoms such as distal polyarthritis, exacerbation of pain in previously compromised joints, and subacute hypertrophic tenosynovitis of the wrist and ankle. Some patients may also have Raynaud's syndrome, depression, fatigue, and weakness. The literature reports a wide symptoms variation from 12 to 18% in South Africa, with 18 months to 2 to 3 years in duration [7,8], 49% in India [9], 80 to 93% in Réunion Island [10]. Another study of the outbreak in India in 2007 reports that the most affected joints were knee (83%) and ankle (63%) [11].

Persistent signs and symptoms include arthritis/arthralgia, edematous polyarthritis of the fingers and toes, morning pain and stiffness, and severe tenosynovitis (especially of the wrists, hands and ankles). Carpal tunnel syndrome may result from hypertrophic tenosynovitis. In addition, patients may report pain in the joints or bones at sites of anterior injury. Occasionally, unusual joints (such as sternoclavicular or temporomandibular joints) are involved. Appearance of Raynaud's phenomenon in the second or third month after infection has been described in up to 20 percent of cases [12]. Cryoglobulinemia has also been found in patients with persistent symptoms attributed to chikungunya [13]. The affected joints do not show radiological changes but there is a report of destructive arthropathy similar to rheumatoid and psoriatic arthritis [14]. The related risk factors were age> 45 years, previous joint disease and severe acute illness [15]. An outbreak study on Mauritius reported persistence of musculoskeletal symptoms in 78.6% of patients in 27.5 months with reported risk factors for advanced age, female gender and initial symmetrical distribution of joint [16].

A recently published follow-up study of patients described the most prevalent symptoms [17]. Joint pains were reported in 32% of cases, musculoskeletal pain also in 32% of patients and 26% had joint edema 9 months after the acute condition. The independent risk factors identified were similar to other studies such as advanced age, female gender in addition to previous musculoskeletal disorders and severe acute symptoms.

Studies in animal models revealed several histopathological alterations similar to those presented by humans as arthritis of mixed inflammatory cells, tenosynovitis and myositis [18].

Chikungunya fever was seen as a self-limiting, benign disease. Reports of recent outbreaks suggest that evolution can follow different paths. Severe complications include respiratory failure, cardiovascular decompensation, myocarditis, acute hepatitis, renal failure, and neurological involvement. Meningoencephalitis is the most common neurological complication. Other manifestations include acute flaccid paralysis and Guillain-Barré syndrome [19]. Ocular manifestations [20] (iridocyclitis, retinitis, episcleritis, macular choroiditis) and hearing loss [21] have also been described. One study described extensive necrosis of the nose skin in three severely ill adults [22]. In Reunion the estimated incidence of serious illness (e.g. patients with complications such as respiratory failure, meningoencephalitis, acute hepatitis or hospitalized renal failure) was 17 per 100.000 population [23].

Pathogenesis

The pathogenesis of severe and persistent joint symptoms that characterize chikungunya virus infections is uncertain. Some data suggest that macrophage-derived products such as tumor necrosis factor-alpha (TNF α), interferon-gamma (IFN γ), and macrophages chemoattractant protein-1 (MCP 1) may play important roles in joint tissue damage [24].

The pathogenesis of CHIKV infection in humans is still poorly understood, but recent outbreaks have provided insight into the cells and organs involved in viral replication. CHIKV can replicate in human epithelial cells and endothelial cells, primary fibroblasts and, to a lesser extent, macrophages derived from monocytes [25]. In contrast, CHIKV does not replicate in lymphoid tissue and monocyte cell lines, lymphocytes and primary monocytes or dendritic cells derived from monocytes. Immunological studies in muscle biopsies from patients infected with CHIKV with myositis syndrome presented viral antigens exclusively within skeletal muscle progenitor cells (designed as satellite cells) rather than on muscle fibers. CHIKV can replicate and induce cytopathic effect in human satellite cells, while myotubes are essentially refractory to infection. Interestingly, CHIKV was detected in these cells during the acute and recurrent phase (3 months after initial infection). Although CHIKV is not a neurotropic virus, there is evidence to support neurological involvement, although molecular mechanisms have not been investigated [26].

CHIKV infection causes strong innate responses, mainly involving the production of antiviral IFN-α, as well as many pro-inflammatory cytokines, chemokines and growth factors [27]. This innate response is followed by the activation of adaptive immunity through the activation and proliferation of CD8 + T cells in the early stages of the disease. Late stages of the acute phase are characterized by a classic disruption of the CD4 + T cell response and the production of anti-inflammatory proteins of IL-1Ra and IL-2RA. Contrary results have been found between the correlation of viremia and levels of IFN-α. During typical CHIKV infection, strong production of IFN-α may be crucial in the rapid control of viremia. CHIKV infection induces a strong inflammatory response that can be orchestrated through the production of IL-16, IL-17, monocyte chemoattractant protein 1 (MCP-1), Interferon gamma-induced protein 10 (IP-10) and macrophage inflammatory proteins (MIP-1α). The end of the acute phase is characterized by the production of proinflammatory substances such as migration inhibitory factor (MIF), MIP-1b, Stromal cell-derived factor 1a (SDF-1a) and IL-6 and IL-8. Elevated levels of C-C chemokine receptor type 5 (CCL5) were also found in all patients during the first week after the onset of symptoms. CCL5, MCP-1, IP-10, MIP-1b and IL-8 are produced by activated macrophages that are susceptible to CHIKV infection. These chemokines play an important role in the recruitment of leukocytes to sites of infection, as well as to orchestrate the effective antiviral defense.

CHIKV infection also induces strong cellular immune responses. Elevated plasma levels of IFN-γ, IL-4, IL-7 and IL-12 and cytokines that promote adaptive immunity, suggest involvement of cellular responses. A key role for NK (natural killers) cells in clearance of infect-

ed cells and the development of arthralgia has also been suggested. B-cell, IL-4 and, in some cases, IL-10, cytokines are upregulated within the first few days after onset of symptoms and may increase CHIKV specific IgG production. CD4 + T lymphocytes, which are also involved in promoting humoral responses and are strongly activated towards the end of the acute phase. IgG antibodies are detected in the first week after infection, indicating rapid seroconversion and elevated levels of antibody responses in CHIKV-infected individuals. IgM and IgG antibodies persist for 4-6 months in patients infected with CHIKV. However, its role in chronic arthralgia is not very well understood [28].

Chikungunya infection induces innate and morphometric immune activation of astrocytes in vivo. The altered glia-neuron signaling may be an important driving factor in the development of the chikungunya associated neuropathology [29].

Diagnosis

Diagnostic techniques for the identification of the chikungunya virus include serology, viral culture and molecular techniques [30]. Serology is the main tool for diagnosis in clinical practice. Immunoglobulin M (IgM) from chikungunya virus antibodies (detected by enzyme-linked immunosorbent assay -ELISA) is present in about five days (range 1 to 12 days) after the onset of symptoms and persists for several weeks at three months. Immunoglobulin G (IgG) antibodies start appearing about two weeks after the onset of symptoms and may persist for years. In endemic areas, chikungunya infection may be suspected based on usual clinical findings during outbreaks. In places that do not have adequate laboratories, many infections can remain undiagnosed. Viral culture and molecular techniques are important research tools. Chikungunya viruses can be isolated from the blood during the first week of disease using culture in mosquito cells, mammalian cells (Vero) or in rats. The sensitivity of viral culture is high in early infection but falls five days after disease onset. Chikungunya virus RNA can also be detected by RT-PCR during the first five days after onset of symptoms with excellent sensitivity and specificity [31]. Virus isolation allows identification of the viral strain and may be important for research and epidemiological purposes, but RT-PCR is faster than the culture with a higher sensitivity and specificity.

The differential diagnosis should be made with the following diseases: Dengue, Zika virus, seronegative rheumatoid arthritis, enteric fever, leptospirosis, malaria, rubeolla, measles, mononucleosis, meningococcal infection, other infections - acute HIV by ricketsias.

Treatment

Support treatment should be offered to patients suspected of chikungunya fever after differential diagnosis with other diseases. Recent studies in acute phase patients reveal an increase in proinflammatory cytokines including interferon α and γ, interleukins (IL) 2, 2R, 6, 7, 12, 15, 17 and 18 that support the initial conduct of relieving fever and joint pain with use of antipyretic analgesics (dipyrone and paracetamol) and NSAIDs [32]. Patients with severe pain that do not improve with the usual measures should weigh the risk benefit of the use of opioids and corticosteroids.

Patients with chronic post chikungunya pain for 17 months on Reunion Island demonstrated pain intensity by visual analogue scale (VAS) of 5.8 +/- 2.1 with an average duration of 89 +/- 2 days. 56 patients met criteria for chronic pain. Pain was classified as neuropathic in 18.9% of the cases by the evaluation of the DN4 questionnaire and 65% of the patients with neuropathic pain had chronic pain. Interference of pain in daily living activities calculated by the Brief Pain Inventory (BPI) was significantly higher in patients with chronic pain (6.8 +/- 1.9 vs 5.9 +/- 1.9, $p < 0.05$) and in patients with neuropathic pain (7.2 +/- 1.5 vs 6.1 +/-1.9, $p < 0.05$) [33].

Studies on the indication of chloroquine use for these patients have conflicting results. In 2008, a De Lamballerie study [34] on Reunion Island showed no benefit and another study conducted in India [35] also showed no benefit in using chloroquine despite an initial study in Africa showing benefits [36].

A French group has developed a guideline for the management of acute and chronic chikungunya infections in selected patients that includes various treatment modalities, including steroids, methotrexate and immune modulating agents [37,38]. According to this same French group, approximately 95% of patients who still have pain 3 months after acute infection have varied musculoskeletal symptoms

but no polyarthritis and have substantial improvement with prolonged administration of non-steroidal anti-inflammatory drugs (which strictly limits steroids), analgesics, and local treatment including physical therapy. In contrast, the other 5% of patients who meet the criteria for chronic inflammatory rheumatism (rheumatoid arthritis, spondylarthritis, polyarthritis or unclassified) have a potentially destructive course and require disease-modifying antirheumatic drugs (such as methotrexate). These two diverse profiles of post-chikungunya fever need to be distinguished in the evaluation of therapeutic trials or biomedical studies because the underlying immunological and viral mechanisms differ. An understanding of the pain pathogenesis in chikungunya fever is essential to improve therapeutic strategies for millions of affected patients worldwide [39].

Refractory symptoms may be improved by the use of a short-term systemic or intra-articular steroid [40]. A study conducted on Reunion Island with a 6-year follow-up of 159 patients revealed that 59% of patients who had no previous joint disease developed chronic rheumatoid arthritis (n = 40), spondylarthritis (n = 33) and nonspecific polyarthritis (n = 21). Radiological changes occurred in half of the patients after 3.5 years. Adequate therapeutic response with methotrexate occurred in 75% of patients. 13% of patients used immunomodulatory biological agents due to contraindication to the use of methotrexate [37].

No antiviral agent has been shown to be effective in human infection; Ribavirin and interferon-alpha appear to have activity *in vitro* against virus replication [41]. Chloroquine sulfate has been suggested as a possible treatment because of its anti-inflammatory properties but has not been shown to be effective [42]. Documentation of long-term viral persistence in non-human primates raises questions about the role of immune dysregulation and persistence of the virus in chronic cases [43].

Until now, there is no licensed vaccine for the prevention of chikungunya infection. Current researches are underway to develop a vaccine using variety of approaches [44,45] and monoclonal antibodies for treatment [46]. Recently Weaver has published an article demonstrating the preclinical safety of a vaccine for CHIKV [47].

Conclusion

Analyzing the data, we conclude that a large part of the world's population, particularly in the African continent and the Americas, is exposed to chikungunya virus infection, demanding an intensification of health care programs for these individuals. Recent work estimates that between 2015 and 2016, 385.835 - 429.058 people in the Americas will develop what is called chronic inflammatory rheumatism after chikungunya [48].

The World Health Organization (WHO) has made educational information available to the population and health sectors [49]. The Brazilian public sector has taken some measures to combat the vector throughout the country [50]. In addition to preventive measures, health professionals should be prepared to take care of the chronic pain resulting from this infection. The literature reports show a very large variation in the percentage of cases with chronic pain, from 12% in South Africa to 93% in Reunion Island.

Joint pain should be better studied in order to guide treatment. Some scientific articles point to a neuropathic component but there are indications of a systemic inflammatory component classified as seronegative rheumatoid arthritis [51].

Therapeutic behavior may follow different paths as doubts are clarified. So far, the studies have not been sufficient to point us the direction to be taken: if the 1st line drugs for neuropathic pain (gabapentinoids and antidepressants) or the 2nd line drugs such as immunomodulatory drugs (chloroquine and methotrexate) or biological agents. Another question is whether a multimodal approach (intravenous infusion of lidocaine, ketamine and magnesium) would be effective in these patients. While awaiting the answers, a thorough history and physical examination using tools to define the neuropathic component as DN4 corroborated by laboratory and radiological examinations may guide us in the therapeutic course to be used.

Bibliography

1. Alan L Schmaljohn and David McClain. "Alphaviruses (Togaviridae) and Flaviviruses (Flaviviridae)". Medical Microbiology. 4th edition. Chapter 54.

2. "Fact Sheet Chikungunya Media Center". World Health Organization.

3. Secretaria Vigilância em Saúde - Ministerio da Saúde. Boletim Epidemiológico 48.5 (2017): 3-7.

4. Papadakis M A., *et al*. "Chikungunya Fever". 2017 Current Medical Diagnosis and Treatment. Fifty sixth edition. McGraw Hill Education (2017): 1407.

5. Rajapakse S., *et al*. "Atypical manifestations of chikungunya infection". *Transactions of the Royal Society of Tropical Medicine and Hygiene* 104.2 (2010): 89-96.

6. Economopoulou A., *et al*. "Atypical chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005-2006 outbreak on Réunion". *Epidemiology and Infection* 137.4 (2009): 534-541.

7. Brighton SW., *et al*. "Chikungunya virus infection. A retrospective study of 107 cases". *South African Medical Journal* 63.9 (1983): 313-315.

8. Fourie ED and Morrison JG. "Rheumatoid arthritic syndrome after chikungunya fever". *South African Medical Journal* 56.4 (1979): 130-132.

9. Manimunda SP., *et al*. "Clinical progression of chikungunya fever during acute and chronic arthritic stages and the changes in joint morphology as revealed by imaging". *Transactions of the Royal Society of Tropical Medicine and Hygiene* 104.6 (2010): 392-399.

10. Soumahoro MK., *et al*. "Impact of Chikungunya virus infection on health status and quality of life: a retrospective cohort study". *PLoS One* 4.11 (2009): e7800.

11. A J Mathew., *et al*. "Rheumatic-musculoskeletal pain and disorders in a naıve group of individuals 15 months following a Chikungunya viral epidemic in south India: a population based observational study". *International Journal of Clinical Practice* 65.12 (2011): 1306-1312.

12. Simon F., *et al*. "Chikungunya infection: an emerging rheumatism among travelers returned from Indian Ocean islands. Report of 47 cases". *Medicine (Baltimore)* 86 (2007): 123-137.

13. Liver M., *et al*. "Persisting mixed cryoglobulinemia in Chikungunya infection". PLOS Neglected Tropical Diseases 3.2 (2009): e374.

14. Bouquillard E and Combe B. "Rheumatoid arthritis after Chikungunya fever: a prospective follow-up study of 21 cases". *Annals of the Rheumatic Diseases* 68.9 (2009): 1505-1506.

15. Hoarau JJ., *et al*. "Persistent chronic inflammation and infection by Chikungunya arthritogenic alphavirus in spite of a robust host immune response". *Journal of Immunology* 184.10 (2010): 5914-5927.

16. Khadijah Essackjee., *et al*. "Prevalence of and risk factors for chronic arthralgia and rheumatoid-like polyarthritis more than 2 years after infection with chikungunya virus". *Postgraduate Medical Journal* 89.1054 (2013): 440-447.

17. Cosmina Zeana., *et al*. "Post chikungunya rheumatic disorders in travelers after return from the Caribbean". *Travel Medicine and Infectious Disease* 14.1 (2016): 21-25.

18. Thomas E Morrison, *et al*. "A Mouse Model of Chikungunya Virus-Induced Musculoskeletal Inflammatory Disease Evidence of Arthritis, Tenosynovitis, Myositis, and Persistence". *The American Journal of Pathology* 178.1 (2011): 32-40.

19. Robin S., *et al*. "Neurologic manifestations of pediatric chikungunya infection". *Journal of Child Neurology* 23.9 (2008): 1028-1035.

20. Chanana B., *et al*. "Bilateral macular choroiditis following Chikungunya virus infection". *Eye (London)* 21.7 (2007): 1020-1021.

21. Bhavana K., *et al*. "Chikungunya virus induced sudden sensorineural hearing loss". *International Journal of Pediatric Otorhinolaryngology* 72.2 (2008): 257-259.

22. Torres JR., *et al*. "Nasal Skin Necrosis: An Unexpected New Finding in Severe Chikungunya Fever". *Clinical Infectious Diseases* 62.1 (2016): 78-81.

23. Paquet C., *et al*. "Chikungunya outbreak in Reunion: epidemiology and surveillance, 2005 to early January 2006". *Euro Surveillance* 11.2 (2006): E060202.

24. Lidbury BA, *et al*. "Macrophage-derived proinflammatory factors contribute to the development of arthritis and myositis after infection with an arthrogenic alphavirus". *Journal of Infectious Diseases* 197.11 (2008): 1585-1593.

25. Sourisseau M., *et al*. "Characterization of re-emerging chikungunya virus". *PLoS Pathogens* 3.6 (2007): e89.

26. Arpino C., *et al*. "Chikungunya and the nervous system: what we do and do not know". *Reviews in Medical Virology* 19.3 (2009): 121-129.

27. Wauquier N., *et al*. "The acute phase of chikungunya virus infection in humans is associated with strong innate immunity and T CD8 cell activation". *Journal of Infectious Diseases* 204.1 (2011): 115-123.

28. Aoyama I., *et al*. "A case of chikungunya fever imported from India to Japan, follow-up of specific IgM and IgG antibodies over a 6-month period". *Japanese Journal of Infectious Diseases* 63.1 (2010): 65-66.

29. Inglis FM, *et al*. "Neuropathogenesis of Chikungunya infection: astrogliosis and innate immune activation". *Journal of NeuroVirology* 22.2 (2016): 140-148.

30. Lakshmi V, *et al*. "Clinical features and molecular diagnosis of Chikungunya fever from South India". *Clinical Infectious Diseases* 46.9 (2008): 1436-1442.

31. Panning M., *et al*. "Chikungunya fever in travelers returning to Europe from the Indian Ocean region, 2006". *Emerging Infectious Disease* 14.3 (2008): 416-422.

32. Teng TS., *et al*. "A Systematic Meta-analysis of Immune Signatures in Patients with Acute Chikungunya Virus Infection". *Journal of Infectious Diseases* 211.12 (2015): 1925-1935.

33. Andrade DC., *et al*. "Chronic pain associated with the Chikungunya Fever: long lasting burden of an acute illness". *BMC Infectious Diseases* 10 (2010): 31.

34. De Lamballerie X., *et al*. "On chikungunya acute infection and chloroquine treatment". *Vector-Borne and Zoonotic Diseases* 8.6 (2008): 837-839.

35. Chopra A., *et al*. "Effectiveness of chloroquine and inflammatory cytokine response in patients with early persistent musculoskeletal pain and arthritis following chikungunya virus infection". Arthritis and Rheumatology 66.2 (2014): 319-326.

36. Brighton SW. "Chloroquine phosphate treatment of chronic Chikungunya arthritis. An open pilot study". *South African Medical Journal* 66.6 (1984): 217-218.

37. Javelle E, *et al*. "Specific management of post-chikungunya rheumatic disorders: a retrospective study of 159 cases in Reunion Island from 2006-2012". *PLOS Neglected Tropical Diseases* 9.3 (2015): e0003603.

38. Simon F, *et al*. "French guidelines for the management of chikungunya (acute and persistent presentations)". November 2014". *Medecine Et Maladies Infectieuses* 45.7 (2015): 243-263.

39. Fabrice Simon., *et al*. "Chikungunya Virus Infections". *New England Journal of Medicine* 373.2 (2015): 93-95.

40. Sissoko D., *et al*. "Post-epidemic Chikungunya disease on Réunion Island: course of rheumatic manifestations and associated factors over a 15-month period". *PLOS Neglected Tropical Diseases* 3.3 (2009): e389.

41. Briolant S., *et al*. "In vitro inhibition of Chikungunya and Semliki Forest viruses replication by antiviral compounds: synergistic effect of interferon-alpha and ribavirin combination". Antiviral Research 61.2 (2004): 111-117.

42. Savarino A, *et al*. "On the use of chloroquine for Chikungunya". *Lancet Infectious Diseases* 7.10 (2007): 633.

43. Labadie K., *et al*. "Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages". *Journal of Clinical Investigation* 120.3 (2010): 894-906.

44. Edelman R., *et al*. "Phase II safety and immunogenicity study of live chikungunya virus vaccine TSI-GSD-218". *American Journal of Tropical Medicine and Hygiene* 62.6 (2000): 681-685.

45. Ramsauer K., *et al*. "Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active-comparator, first-in-man trial". *Lancet Infectious Diseases* 15.5 (2015): 519-527.

46. Fric J., *et al*. "Use of human monoclonal antibodies to treat Chikungunya virus infection". *Journal of Infectious Diseases* 207.2 (2013): 319-322.

47. Plante KS., *et al*. "Extended Preclinical Safety, Efficacy and Stability Testing of a Live-attenuated Chikungunya Vaccine Candidate". *PLOS Neglected Tropical Diseases* 9.9 (2015): e0004007.

48. Rodriguez-Morales AJ., *et al*. "How many patients with post-chikungunya chronic inflammatory rheumatism can we expect in the new endemic areas of Latin America". *Rheumatology International* 35.12 (2015): 2091-2094.

49. Media Center - Chikungunya - Fact Sheet 327.

50. Prevenção e Combate - Dengue, Chikungunya e Zica.

51. Miner JJ., *et al*. "Chikungunya viral arthritis in the United States: a mimic of seronegative rheumatoid arthritis". Arthritis and Rheumatology 67.5 (2015): 1214-1220.

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