REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO

JOURNAL OF THE SÃO PAULO INSTITUTE OF TROPICAL MEDICINE

http://doi.org/10.1590/S1678-9946202365026

Hydroxychloroquine for the management of chronic chikungunya arthritis

Fortaleza, January 30th, 2023

Dear Editor

Chikungunya fever is a zoonotic viral disease transmitted by infected *Aedes* spp. mosquitoes with epidemic potential. It is an important cause of morbidity in developing countries, presenting with high fever, maculopapular rash, polyarthralgia, and myalgia in the acute phase. Many joint-related symptoms persist beyond the initial manifestations of the disease, leading to chronic pain and significant functional impairment[1]. In 2022, there were more than 173,000 probable cases of chikungunya (incidence rate of 81.2 cases per 100,000 inhabitants) in Brazil, an increase of 78.2% compared to the previous year. Until now, 93 deaths from chikungunya have been confirmed in the country, most of them (41.9%) in the Ceara State[2]. While the acute phase is due to viremia, the chronic phase (i.e., when symptoms persist for more than three months) is believed to be an autoimmune phenomenon with up to 83% of patients reporting persistent joint pain[3,4].

Regarding clinical characteristics, chronic chikungunya arthritis (CCA) can mimic many rheumatic conditions, being particularly similar to rheumatoid arthritis (RA). The similarities between CCA and RA include a predominance among middle-aged women, elevation of acute phase reactants, radiological changes, symmetric involvement of small peripheral joints, and a good response to immunosuppressive treatment[5,6].

In some cases, it can be difficult to determine whether the virus played a role in triggering RA or whether the symptoms are only part of the chronic phase of chikungunya. The similarities also extend to pathogenesis, given the parallel high levels of circulating pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, IL-17, and tumor necrosis factor (TNF), as well as the types of immune cells involved in perpetuating inflammation and joint destruction, such as fibroblast-like synoviocytes[5,6]. These pathological similarities support the fact that CCA seems to respond to effective treatment for RA[6]. Methotrexate (MTX), one of the pillars for RA treatment[7], shows a positive response in patients with CCA. Its efficacy, safety, and availability are emphasized by an emerging body of evidence supporting its use at low doses in CCA[5,8].

International guidelines are not consensual regarding the best treatment strategy for CCA. Recently, Webb *et al.*[9] published a systematic review of clinical management guidelines for chikungunya globally. Heterogeneous recommendations prevail, but the majority of medical guidelines (65%, 17/28) consider the disease-modifying antirheumatic drugs (DMARDs) useful for the treatment of CCA. Most of them (65%, 11/17) point to MTX as the first-line therapy, while others (24%, 4/17) recommend antimalarials, such as hydroxychloroquine (HCQ) and chloroquine[9].

The Brazilian Department of Health has released official recommendations in favor of the use of HCQ as first-line therapy for the treatment of CCA[10]. Antimalarial drugs have well-known effects and are widely used in some rheumatic diseases[11]. However, to the best of our knowledge, few published articles analyze the efficacy of antimalarials for CCA. Table 1 shows studies that address the use of these agents, alone or in association with other drugs, for CCA[12-16]. It should be noted that all of

[1]Universidade Federal do Ceará, Faculdade de Medicina, Departamento de Medicina Clínica, Fortaleza, Ceará, Brazil

[2]Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, Serviço de Reumatologia, São Paulo, São Paulo, Brazil

[3]Universidade Federal do Ceará, Faculdade de Medicina, Departamento de Saúde Comunitária, Divisão de Doenças Infecciosas, Fortaleza, Ceará, Brazil

[4]Hospital São José de Doenças Infecciosas, Fortaleza, Ceará, Brazil

[5]Centro Universitário Christus, Faculdade de Medicina, Fortaleza, Ceará, Brazil

Correspondence to: Jobson Lopes de Oliveira
Centro Universitário Christus, Faculdade de Medicina, Rua João Adolfo Gurgel, 133, CEP 60190-060, Fortaleza, CE, Brazil
Tel: +55 85 3265-8153

E-mail: jobsonlopesdeoliveira@gmail.com

Received: 30 January 2023

Accepted: 28 February 2023

Table 1 - Comparison of studies that analyze the efficacy of antimalarials in joint symptoms of chikungunya arthritis.

Article / Year	Study design / Setting / Participants	Treatment / Control	Conclusions	Limitations
Pandya[12] / 2008	Observational India 149 patients	Observational study: Combination of MTX + HCQ	About half of the patients who received the combination of methotrexate and hydroxychloroquine achieved an ACR 20 response at 16 weeks.	Lack of isolation of CHIKV, observational study
Padmakumar *et al.*[13] / 2009	RCT India 120 patients	Aceclofenac alone vs. Aceclofenac + HCQ vs. Aceclofenac and prednisolone vs. Aceclofenac + prednisolone + HCQ	Hydroxychloroquine offers no therapeutic advantage in chikungunya arthritis. Co-administration of low doses of systemic corticosteroids with NSAIDs led to improved pain relief.	High rate of seronegativity, use of clinical methods for diagnosis, included only patients with acute chikungunya arthritis.
Ahmed *et al.*[14] / 2012	RCT India 86 patients	HCQ vs. Paracetamol	Chloroquine is more efficient in reducing the pain of chronic chikungunya arthritis when compared to paracetamol.	High risk of bias regarding blinding, selective reporting, and presenting data.
Chopra *et al.*[15] / 2014	RCT India 70 patients	Chloroquine vs. Meloxicam	No advantage of chloroquine over meloxicam.	Small sample, lack of isolation of CHIKV.
Ravindran *et al.*[16] / 2017	RCT India 72 patients	HCQ vs. HCQ + MTX + SSZ	MTX, SSZ and HCQ are superior to monotherapy with HCQ.	Use of clinical methods for diagnosis, unblinded assessments, use of outcome measures not validated for chikungunya arthritis.

ACR = American College of Rheumatology; CHIKV = chikungunya virus; DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; MTX = methotrexate; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial; SSZ = sulfasalazine.

these studies have major limitations, such as the use of clinical methods for diagnosis instead of serology; small samples in each arm; the fact that most were located in a single country; and the heterogeneity of objectives and measures.

Overall, HCQ and chloroquine are safe drugs, with few side effects and most are related to long-term use. However, even though it may be a safe option, the recommendation of a drug should follow evidence-based guidelines, and it seems that the use of antimalarials for CCA is an extrapolation of their effect on other chronic inflammatory rheumatic diseases. Well-designed, randomized, multicenter clinical trials are paramount to evaluate the role of HCQ as the medication of choice for the treatment of patients with chikungunya arthritis.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to the manuscript.

CONFLICT OF INTERESTS

The authors declare to have no conflict of interests.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

Igor Albuquerque Nogueira[1]
Rafael Alves Cordeiro[2]
Guilherme Alves de Lima Henn[3,4]
Jobson Lopes de Oliveira[1,5]

REFERENCES

1. Vairo F, Haider N, Kock R, Ntoumi F, Ippolito G, Zumla A. Chikungunya: epidemiology, pathogenesis, clinical features,

management, and prevention. Infect Dis Clin North Am. 2019;33:1003-25.

2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Monitoramento dos casos de arboviroses até a semana epidemiológica 51 de 2022. Bol Epidemiol. 2022;53:1-35. [cited 2023 Feb 28]. Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/epidemiologicos/edicoes/2022/boletim-epidemiologico-vol-53-no48
3. Bouquillard E, Fianu A, Bangil M, Charlette N, Ribéra A, Michault A, et al. Rheumatic manifestations associated with Chikungunya virus infection: a study of 307 patients with 32-month follow-up (RHUMATOCHIK study). Joint Bone Spine. 2018;85:207-10
4. Khongwichit S, Chansaenroj J, Chirathaworn C, Poovorawan Y. Chikungunya virus infection: molecular biology, clinical characteristics, and epidemiology in Asian countries. J Biomed Sci. 2021;28:84.
5. Amaral JK, Bingham CO 3rd, Taylor PC, Vilá LM, Weinblatt ME, Schoen RT. Pathogenesis of chronic chikungunya arthritis: resemblances and links with rheumatoid arthritis. Travel Med Infect Dis. 2022;52:102534.
6. Amaral JK, Bilsborrow JB, Schoen RT. Chronic chikungunya arthritis and rheumatoid arthritis: what they have in common. Am J Med. 2020;133:e91-7.
7. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA. 2018;320:1360-72.
8. Amaral JK, Sutaria R, Schoen RT. Treatment of chronic chikungunya arthritis with methotrexate: a systematic review. Arthritis Care Res (Hoboken). 2018;70:1501-8.
9. Webb E, Michelen M, Rigby I, Dagens A, Dahmash D, Cheng V, et al. An evaluation of global Chikungunya clinical management guidelines: a systematic review. EClinicalMedicine. 2022;54:101672.
10. Brasil. Ministério da Saúde. Departamento de Vigilância das Doenças Transmissíveis. Febre de chikungunya: manejo clínico. Brasília: Ministério da Saúde; 2015. [cited 2023 Feb 28]. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/febre_chikungunya_manejo_clinico.pdf
11. Reis Neto ET, Kakehasi AM, Pinheiro MM, Ferreira GA, Marques CD, Mota LM, et al. Revisiting hydroxychloroquine and chloroquine for patients with chronic immunity-mediated inflammatory rheumatic diseases. Adv Rheumatol. 2020;60:32.
12. Pandya S. Methotrexate and hydroxychloroquine combination therapy in chronic chikungunya arthritis: a 16 week study. Indian J Rheumatol. 2008;3:93-7.
13. Padmakumar B, Jayan JB, Menon RM, Krishnankutty B, Payippallil R, Nisha RS. Comparative evaluation of four therapeutic regimes in chikungunya arthritis: a prospective randomized parallel-group study. Ind J Rheumatol. 2009;4:94-101.
14. Ahmed M, Shantharam N, Redd YJ. Randomized clinical trial in chikungunya arthritis cases. J Evol Med Dent Sci. 2012;1:841-7.
15. Chopra A, Saluja M, Venugopalan A. Effectiveness of chloroquine and inflammatory cytokine response in patients with early persistent musculoskeletal pain and arthritis following chikungunya virus infection. Arthritis Rheumatol. 2014;66:319-26.
16. Ravindran V, Alias G. Efficacy of combination DMARD therapy vs. hydroxychloroquine monotherapy in chronic persistent chikungunya arthritis: a 24-week randomized controlled open label study. Clin Rheumatol. 2017;36,1335-40.