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Review

Treatment of chikungunya musculoskeletal disorders: a systematic review

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Abstract

Introduction: Chikungunya virus is amongst the fastest expanding vector transmissible diseases in recent years and has been causing massive epidemics in Africa, Asia, Latin America and the Caribbean. Despite human infection by this virus being first described in the 1950s, there is a lack of adequate therapeutic evaluations to guide evidence-based recommendations. The current guidelines rely heavily in specialists' opinion and experience instead of using higher rated evidence.

Areas covered: A systematic review of the literature was performed- not restricted to clinical trials - reporting the therapeutic response against this infection with the intent to gather the best evidence of the treatment options against musculoskeletal disorders following chikungunya fever. The 15 studies included in the analysis were categorized considering the initiation of treatment during the acute, subacute and chronic phase.

Expert Commentary: This review demonstrates the complexity of chikungunya fever and difficulty of therapeutic management. This review found no current evidence-based treatment recommendations for the musculoskeletal disorders following chikungunya fever. To provide an optimal treatment that prevents perpetuation or progression of chikungunya infection to a potentially destructive and permanent condition without causing more harm is an aim that must be pursued by researchers and health professionals working with this disease.

Keywords: Chikungunya fever, musculoskeletal disorders, treatment, systematic review, therapeutic evaluation

1. Introduction

Chikungunya fever (CHIKF) is a disease caused by the chikungunya virus (CHIKV), a RNA virus of the *Togaviridae* family and the Alphavirus genus. It is transmitted particularly by the bite of *Aedes aegypti* and *Ae. albopictus* mosquitoes [1]. Before 2000, large CHIKF outbreaks were rare, but since then, some genetic studies have suggested that there has been an evolutionary adaptation of the virus to vectors [2, 3], mainly to *Ae. albopictus*, contributing to the reemergence of the virus and contributing to large-scale epidemics in several parts of the world since 2004 [4].

CHIKV was first detected in the Region of the Americas in October 2013 on the island of Saint-Martin, Caribbean region. In February 2014, the virus spread to several other islands in the Caribbean, as well as South American countries becoming a major public health problem [5].

The chikungunya acute phase (the first three weeks of symptoms) is characterized by sudden onset of high fever, headache, arthralgia, myalgias, and a macular or popular rash. The main characteristic of CHIKF is the presence of polyarthralgia/arthritis described in more than 90% of the patients in the acute phase of the disease, generally symmetrical and associated with edema. Edema, when present, is usually associated with tenosynovitis [5]. The joints of hands, wrists, elbows, knees, ankles and feet are the most affected [5]. Axial involvement can occur in up to half of infected individuals. There may be associated cervical lymphadenomegalies [6] and some patients evolve with atypical severe manifestations such as neuritis, encephalitis and myocarditis [5].

After the acute or febrile phase, some patients evolve with persistent joint pain, characterizing the onset of the subacute phase, lasting up to 3 months [5]. During this phase, fever usually disappears and there may be persistence or worsening of arthralgia, including distal polyarthritis, exacerbation of joint pain in regions previously affected in the first stage,

and subacute hypertrophic tenosynovitis on wrists and ankles [5]. Articular and periarticular involvement is usually accompanied by edema of varying intensity.

Joint and periarticular involvement is often debilitating and categorized as chronic if persisting beyond three months after symptoms onset, and can last for months and even years [1]. Joint pain during this phase may be the result of mechanical musculoskeletal disorders or inflammatory manifestations such as synovitis and tenosynovitis. Enthesopathy may present with a fluctuating and migratory course. A few patients may develop a destructive arthropathy like psoriatic or rheumatoid arthritis. Patients may also present a variety of manifestations such as fatigue, headache, pruritus, alopecia, rash, bursitis, tenosynovitis, dysesthesia, paresthesia, neuropathic pain, Raynaud's phenomenon, cerebellar alterations, sleep disorders, memory disorders, attention deficit, alterations mood, visual turbidity and depression. This phase can last up to three years and prevalence varies among the studies [6,7,8].

Studies suggest that the likelihood of articular chronicity is associated with older age, presence of previous joint disease, such as osteoarthritis, intensity of pain during the acute phase, viral load and titration of IgM antibodies and with the involvement of different joints in the initial phase of the disease [8, 9]. This chronic joint condition interferes with the patient's quality of life, functional and work capacity. By reducing the patient's productivity, CHIKF may place a significant burden on both society and patient in terms of economic impact [10].

The management of a patient with CHIKF varies according to the stage of the disease [6]. During the acute phase, common analgesics (i.e. paracetamol) and opioids are commonly prescribed, according to the intensity of pain. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are avoided at this stage of the disease but are commonly used in the subacute and chronic phases. Some antivirals present in vitro and in vivo activity,

though they have not been evaluated in clinical trials [11]. In the lack of high-strength evidence against CHIKF musculoskeletal manifestations, most recommendations have adopted therapies used for more common inflammatory arthropathies, with the use of chloroquine derivatives and disease modifying anti-rheumatic drugs (DMARDs). Such variety demonstrates the important gap on evidence on how to better manage CHIKV [12,13,14,15,16,17,18,19,20]. Biologic DMARD (bDMARD) have also been used to treat refractory cases of chronic arthritis [12,17,19]. For patients with severe neuropathic pain, amitriptyline hydrochloride, gabapentin or pregabalin may be combined with the analgesics being used. [5, 21].

Prevalence of post-chikungunya infection chronic inflammatory arthritis [22], CHIKV cardiovascular involvement [23] and long-term sequelae of CHIKV [24] were recently systematic reviewed. Although the study of Marimoutou et al [25] has shown a six-year follow-up of patients exposed to the chikungunya virus, the data on treatment of all chikungunya disease phases including the induced chronic arthritis are limited. Very few randomized trials assessing the efficacies of different therapies are available. Consequently, there is a lack of adequate therapeutic evaluations. This results in the currently available management guidelines relying in specialists' opinion and experience instead of using higher rated evidence.

We performed a systematic review of the available literature reporting on the evaluation of therapeutic response against this infection with the intent to gather the best evidence to critically evaluate the treatment options against musculoskeletal disorders following CHIKF.

2. Methods

2.1 Search

This review was performed with a pre-established protocol and described according to the recommendations of the PRISMA statement [26]. A systematic search was conducted in Medical Literature Analysis and Retrieval System Online (Medline), Latin American and Caribbean Health Sciences Literature (Lilacs), Excerpta Medical Database (Embase), Cochrane Library, Google Scholar to identify studies assessing management of musculoskeletal disorders in laboratory confirmed chikungunya patients published up to 30th July 2017. Additionally, references of the revised articles were also screened for eligibility.

The search descriptors used for Medline were as follows: “chikungunya virus”, “chikungunya fever” and “treatment”, “drug therapy”, “therapy”, “management”, “intervention” and “adult”, “aged”, “humans”. The search strategy was adapted according to the characteristics of each database. The complete search strategies used are presented in Additional file 1. There were no language restrictions in the searches on databases.

2.2 Selection

The selection was performed by two authors independently (CSB and HFPS). Studies were included if reporting data allowing the assessment of therapies targeting musculoskeletal manifestations of CHIKF in patients ≥ 18 years-old (yo) with laboratory confirmed diagnosis. First, the titles and abstracts retrieved by the search were read. Articles that were guidelines reports, editorials, letters, reviews, congress presentations; immunologic studies, and studies with no treatment described were excluded. Secondly, studies potentially eligible for inclusion were read in full by the same two reviewers, and the inclusion determined by discussion and consensus.

2.3 Data extraction and Quality assessment

Data were extracted by two of the authors (CSB and HFPS) independently. Discrepancies were reviewed and decided by consensus reached between three authors (PB, MDW, LG). A standardized data extraction form was elaborated for the review, including the following sections: identification of the study (authors, journal and year of publication, language); studies characteristics (design, total number of patients, period); study population (age, sex, setting, chikungunya diagnostic method, clinical features); therapy – pharmacologic (drugs, posology, time of treatment, indication/disease stage) or non-pharmacologic, outcomes and effectiveness. The form is available from the authors upon request.

Assessment of the methodological quality of the included studies was based on the Methodological Index for Non-randomized Studies (MINORS) for observational studies. The instrument consists of 12 items, the first eight being specific for non-comparative studies [27]. Cochrane Risk of Bias Tool for Randomized Controlled Trials was used for clinical trials. It consists of seven items to assess trials according to Cochrane Handbook for Systematic Reviews of Interventions Version [28]. Two authors (MDW, LG) evaluated each article independently and the disagreements were resolved by consensus.

2.4 Data Synthesis and Analysis

A description of the studies regarding country, population, disease onset, clinical features, treatment, drugs used, outcomes and effectiveness of pharmacologic treatments observed within 3 weeks and in more than 3 weeks after the onset of symptoms was performed.

3. Results

In the initial screening of papers following the search criteria, 198 studies were revised, resulting in 15 articles filling the inclusion criteria which were, therefore, included in the analysis [figure 1].

The included articles were published between 2007 and 2017. There was a predominance of countries where there is active transmission of CHIKV together with reports from accounts from travel medicine centres in non-endemic countries. Regarding study design, 12 studies (80%) were observational, most of them case reports or case series, and three (20%) clinical trials. The included studies were performed in adults, where there was an overall predominance of females [table 1].

The quality of articles was assessed by Minors instrument for all observational studies except for case reports. All studies presented endpoints appropriate to their aim and about two thirds reported prospective collection data and follow-up period appropriate. More than half of studies did not report the inclusion of consecutive patients [figure 2].

Two trials included in the revision [12, 13] achieved poor quality by Cochrane Risk of Bias tool. They had high risk of bias at selection bias domain (allocation concealment issue), performance bias and detection bias domains respectively. The trial of Chopra et al [14] achieved fair quality classification and had unclear risk at the election bias domain (random sequence generation and allocation concealment issues).

Among the studies, five [29-33] (33.3% of all) started following patients within 3 weeks of symptom onset, describing mostly acute phase manifestations. Two studies, by Malvy and Ravindran [34, 12], started following patients with more than one year of musculoskeletal symptoms.

A single selected study [29] described other manifestations than musculoskeletal symptoms. One study (Simon) did not restrict the description of musculoskeletal symptoms,

also describing other manifestations such as one patient out of 47 with transient myocarditis and two with bilateral conjunctivitis.

In the description of the treatment given to study subjects, complete information regarding the name of the drug administered, dose information, route of administration, adverse effects and length of treatment were reported by 9 studies [12, 13, 14, 15, 16, 32, 34, 35, 36] [Table 1], while the use of non-pharmacological therapies (acupuncture, physiotherapy, diet or supplementation vitamins) were described in two [17, 37]. Corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) were reported in 66% of the studies. DMARDs were described in 53.3% of the studies including chloroquine/hydroxychloroquine in 46.6%, sulfasalazine and methotrexate in 26.7%, leflunomide in 13.3%, etanercept and adalimumab in two studies, and rituximab, tocilizumab, infliximab, golimumab, abatacept in one study each. General analgesics use was reported in 27% and immunosuppressants in 13.3% of the studies reviewed. Colchicine was reported in two studies [17, 36] while the use of antivirals, antidepressants, antiepileptics and antineoplastics was described in one article each [17, 35, 37] [Table 2].

Nine studies used standard quantitative measures (visual scales, clinical scores, structured questionnaires, laboratory and imaging exams) to measure outcomes such as pain, joint involvement, quality of life and functional capacity [12, 13, 14, 15, 16, 17, 34, 35, 37]. The others described clinical improvement criteria evaluated by the doctor or self-reported by patients. In addition, the occurrence of clinical relapse among patients after discontinuation of therapy was referred in a single study [17] [Table 2].

Effectiveness was assessed either by clinical improvement or by specific clinical scores according to the author's criteria. The overall effectiveness was shown as 50 to 100% among patients treated up to 3 weeks (≤3 weeks) of symptoms, 70% in patients with more than 3 weeks to less than 3 months (>3weeks to <3 months) and 12.5% to 100% in the group

with more than 3 months of symptoms (≥3 months). Time of improvement was described in nine studies: 3 days to 1 month (≤3 weeks), 6 weeks (>3weeks to <3 months) and 4 to 8 months (≥3 months) [14, 16, 29, 30, 31, 32, 33, 34, 36] [Table 2].

4. Discussion/Conclusion

In Latin America and Caribbean, 1.9 million of people have been infected by CHIKV since 2014 [39] and half of the infected people may present persisting disorders that can last for months to years [40]. Several tourists from non-endemic regions are also under risk of infection when visiting endemic countries [41].

After a search covering the last ten years, in a range of database, with no restriction of language nor study, we were not able to identify high quality evidence to guide treatment recommendations for the musculoskeletal disorders following CHIKF.

We opted to take a broader look at the available evidence in the field and not restrict the review to clinical trials as previous attempts clearly pointed to the lack of such studies – only three trials identified in our search strategy – and would substantially limit our evaluation. To minimize the risk of biases related to observational studies, we applied a stringent inclusion criteria and applied a thorough analysis of the quality of studies [Figure 2], resulting in only 15 studies being included in our review. We also opted to categorize the studies considering the initiation of treatments evaluation during the acute phase – under three weeks of onset of symptoms – the subacute, (≥ 3 weeks and < 3 months), and chronic phase (≥ 3 months), following the currently used classification criteria. This classification is simple, helps health professionals from around the world to categorize and report patients in a common way and assists the choice of clinical management strategies, independently of being an expert.

Five articles described the effect of therapies given during the acute phase of CHIKF: three case reports and two case series explored the use of analgesic, NSAIDs and corticosteroids effects in the clinical outcome [29,30,31,32,33]. No pain relief or partial clinical improvement was observed with paracetamol, analgesics and short-term systemic NSAIDs. Most patients with tenosynovitis were poorly responsive to NSAIDs but dramatically improved after short-term systemic corticosteroids, although some patients experienced a painful relapse a few days after discontinuation. The authors warned of the risk of severe adverse effects such as aspirin-induced bleeding or paracetamol-induced fulminant hepatitis in elderly or in patients with comorbidity as those with underlying chronic liver disease [29].

One of the main caveats of the evaluation of the efficacy/effectiveness of therapeutic interventions during the acute phase of CHIKF is the definition of outcomes and how they should be measured, what results from the wide spectrum of clinical manifestations. In a nutshell, acute CHIKF outcomes can involve intensity of the clinical symptoms such as joint pain and inflammation, the risk of severe complications such as encephalitis and death or the risk of prolonged joint compromise. For all these possibilities, it is important to adequately choose the measurement instruments for clarity and comparability as the musculoskeletal compromise can encompass many domains of relevance, each requiring its specific tools, as didactically presented by the OMERACT (Outcomes Measurement in Rheumatology) initiative [42].

Despite the improvement of disease symptoms and lower rates of persistence of joint pain with the use of corticosteroids [13], the use of this class of drugs is not recommended in the acute phase in most guidelines of treatment [43,44,45]. This is probably related to fear of the recurrence of joint symptoms after withdrawal and the onset of adverse events (such as worsening of underlying osteoporosis mainly in older adults).

Two clinical trials and one case series analyzed different treatments for patients in the subacute phase of the disease, experiencing persistent musculoskeletal pain and/or arthritis. Chloroquine and hydroxychloroquine were evaluated in different contexts, including two clinical trials conducted in India [13,14]. Despite the potential use of chloroquine to treat viruses, and its recognized propriety of inhibiting the production of proinflammatory cytokines [46,47] the reviewed studies did not demonstrate benefit of chloroquine use on neither arthralgia nor cytokine levels compared to meloxicam [14], nor in the improvement of quality of life [13]. The trial conducted by Padmakumar [13] deserves to be commended by comparing diverse drugs and combinations and by using systematic validated measurements, as the Visual Analog Scale for pain (VAS), 20-point modified Barthel Index for Activities of Daily Living (ADL), Instrumental Activities (IADL) and Health Assessment Questionnaire (HAQ score).

A single study evaluated the use of an antiviral, ribavirin, during the subacute phase [35]. The study only included 10 patients and unmatched controls, with an overall positive result, rendering the need for further and more systematic evaluations. Although Ribavirin may have a direct antiviral property against Chikungunya leading to the faster resolution of joint and soft tissue manifestations observed, this improvement could be attributed to the natural history of CHIKF [48].

The transition to chronic CHIKV-induced musculoskeletal disorders usually with time of symptoms longer than three months, is a well-known complication, sometimes in the form of nonspecific arthralgia, soft tissue involvement or, more rarely, an inflammatory process suggestive of rheumatoid arthritis, spondyloarthritis or undifferentiated arthritis. Prevalence of persistent musculoskeletal manifestations varies among the studies, from 10 to 80% at 15 to 48 months after the onset of CHIKF [7,8,49,50], what can reflect geographical particularities related to the virus or host characteristics, or due to selection bias. For the

evaluation of treatment effectiveness of these complications, we found 10 observational studies and only one clinical trial.

As most of the patients followed during the chronic phase were in use of NSAIDs (in diverse formulations and posology), it is difficult to estimate its effect, which seems to rely mostly in symptom alleviation and do not seem to influence disease evolution [30]. Corticosteroids were also largely used, either as an option for patients not responding to NSAIDs or systematically to reduce the symptoms or to have its effect on duration of joint compromise. The overall result of corticosteroid use was to promote considerable reduction on the intensity of symptoms [17,29].

Apart from the benefit reported in the clinical trial by Ravindran [12], DMARDs, especially methotrexate, seemed to present benefit to long-term refractory patients in several observational studies with varying rates of success [16,17,29,30,34]. This evidence points to the need to prospectively evaluate how to better deploy this class of drugs for modify disease evolution, either in monotherapy or in combination with other interventions. Immunomodulatory agents prescribed resulted in improvement to some patients [15,17], but it is difficult to reach any conclusion without the use of controls due to the variety of agents used and the diversity of patients' characteristics.

The trial of Ravindran [12] also corroborate with the anterior trial of subacute phase [13] and large observational studies in the chronic phase, at not showing benefit of chloroquine derivatives on disease improvement [17,29]. These studies should be enough to question the placement of this class of drugs on the CHIKF management arsenal, as this drug does not seem to lead to any benefit.

Other observational studies demonstrated that antiepileptics and antidepressants were useful in chronic pain after CHIKF when neuropathic features were identified [17,37]. Colchicine improved a persistent arthralgia and swelling after 2-3 days of treatment in a 65yo

American travel tourist to Indian [36]. Together with non-pharmacological therapies, these interventions were not possible to be properly evaluated, as its administration was not reported in detail nor evaluated with objective measurements.

Studies performed during the chronic phases of CHIKF predominated and used a more diverse set of outcome measurements, from subjective evaluation performed by patients and physicians, to validated scales used in rheumatological assessments (VAS, Disease Activity Score (DAS-28), European League Against Rheumatism of Daily Living (EULAR), Brief pain Inventory (BPI) and Short Form Mc Gill Pain Questionnaire (SF-MPQ) and radiographic evaluations. At first look, the diversity of drug classes prescribed, ranging from analgesics, NSAIDs, corticosteroids, opioids, anticonvulsants, antivirals to monoclonal antibodies prescribed during the chronic phases emphasizes the need for better evidence on how to treat this condition. Many of the difficulties arose from the lack of better data on natural history of the infection as factors associated with persistence of symptoms are not well-known, and the variety of pathophysiological mechanisms that are likely to be involved, as patients with chronic joint pain not always have the classical signs of active inflammation affecting the joints, as seeing in common rheumatological conditions. In the face of the limited pathophysiological mechanism knowledge, the therapeutic strategy adopted in most sites has been to deploy management recommendations used for rheumatoid arthritis and other conditions, with the use of medications such as hydroxychloroquine, methotrexate and immunomodulatory agents.

The main limitation of the studies reviewed is the reduced strength of evidences of effectiveness of the treatment of CHIKF musculoskeletal disorders. Twenty percent of the studies included were clinical trials with high risk of bias, as allocation concealment, blinding of participants and outcomes were lacking. The information about pharmacological treatments was not provided in a standardized and detailed way among the studies included in

this review. The description of the drugs only by the pharmacological classes and the lack of information about the administration routes and duration of treatment limit the comparison between treatments since it affects pharmacokinetic and pharmacodynamics parameters, that compromises effectiveness. The safety profile of treatment regimens, also an important issue of effectiveness, was poorly described in most of the studies. Although most of the drugs used to chikungunya musculoskeletal disorders have been used in clinical practice for a long time, the acceptable limits of safety of treatments should be studied and defined considering the combination of drugs and duration of treatment. Despite the limitations presented, the review including these studies provides a starting point for the consideration in the design of further effectiveness and safety studies and brings important information about treatment management of musculoskeletal disorders following CHIKF.

In conclusion, the range of therapeutic options available from the current recommendations reflect the lack of clarity on how to manage CHIKF in its different phases and highlight the complexity of these diseases. Better understanding of the pathophysiological mechanism and systematic assessment of the clinical compromise is needed for guiding the development of evidence-based recommendations. An effort should also be conducted on the standardization of CHIKF assessment and classification to allow pooled analyses and improve efficiency of therapeutic evaluations that shall include interventions that can modify the natural history of this expanding epidemics with potentially debilitating manifestations.

5. Expert commentary

Our review demonstrates the complexity of CHIKF and how difficult it is for health professionals, especially those without Rheumatology training, to manage patients suffering from debilitating musculoskeletal pain. It is a challenge to characterize through physical

examination, with no imaging exams (US, or MRI) available, the anatomical site and pathological process causing the pain affected patients experience, as it is difficult to identify rheumatic disorders appearing after CHIKF. In daily practice, symptoms such as synovitis can be underreported due to difficult anatomic diagnosis by a non-specialist. Another important difficulty in the management of these patients is to administer and minimize the risks related to self-medication and of drug interactions in the presence of severe manifestations and comorbidities. The high lethality rate observed in CHIKF in some locations may be associated with the abusive and concomitant use of several classes of anti-pain medication, associated with other pre-existing morbidities. To provide an optimal treatment that prevents perpetuation or progression of CHIKV infection to a potentially destructive and permanent condition without causing more harm is an aim that must be pursued by researchers and health professionals working with this disease.

6. Five-year view

The scarce understanding of the pathophysiological mechanisms and heterogeneous clinical classification criteria further impair the development of tailored management strategies for this disease. Case series and observational studies make difficult the evaluation of therapeutic response as CHIKF can progress with cure, although patients experience pain for more than one year rarely becoming spontaneously symptomless [29,51,52,53]. On the other hand, clinical trials of single interventions are difficult to be performed in epidemic situations, as cleared explored elsewhere [54], and would not provide the necessary answer on how to make use of such a diversity of therapeutic possibilities and a wide array of spectrum of manifestations. In this context, one possibility is to make use of platform trials [55]. Such trial design is tailored for the concurrent evaluation multiple treatments and are

faster and more efficient on demonstrating which therapeutic option should be given to specific patients' subgroups [56].

Studies on the correlation between pathophysiological mechanisms and clinical manifestations are also highly needed, with priority on answering questions over virus persistence and immunogenetics and on the clinical spectrum of joint compromise [57,58,59]. Apart from shedding light for possible mechanisms to fight the infection and its consequences, these studies will be of great value at determining biomarkers and clinical outcomes that should be harmonized and adopted to allow for broader comparability between studies from diverse settings.

7. Key Issues

- CHIKF can result in patients suffering from debilitating musculoskeletal pain and disorders of difficult management by the health professionals, especially non-specialists.

- Simple analgesic or NSAIDs may not suffice to achieve pain relief in a great proportion of patients in the initial phases of the disease; severe adverse effects as bleeding may contra-indicate the use of NSAIDs, mainly in areas of co-circulation of CHIKV and dengue fever virus, for which differential diagnosis is difficult in the initial phase. Better drugs and management strategies are needed to treat the acute inflammatory rheumatic manifestations of CHIKV infection.

- Corticosteroids are largely used for patients not responding to NSAIDs or systematically to reduce the symptoms or to reduce the duration of joint compromise. Its use during the acute phase has not been recommended by the specialists due to

fears of severe adverse events, and recurrence of joint symptoms after withdrawal, with more studies needed.

- Hydroxychloroquine has been prescribed alone or in combination with others drugs to treat chronic persistent chikungunya arthritis, in overall without showing clear benefits, suggesting it does not work for this disease.

- Studies aimed at validating the efficacy of the early use of MTX, as well as other conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) and long-term corticotherapy, to prevent joint damage is recommended during the chronic phase. These studies should harmonize outcomes measurement and evaluation for comparability.

- There are several gaps in knowledge regarding natural history, epidemiology and pathophysiological mechanisms of CHIKV infection, encompassing, consequently, the lack of adequate therapeutic evaluations. This results in the currently available management guidelines relying upon specialists' opinion and experience instead of using higher rated evidence.

- Case series and observational studies make difficult the evaluation of therapeutic response as CHIKF can progress with cure.

- Clinical trials, difficult to be performed in epidemic situations, provide insufficient evidence to draw conclusions about the efficacy or safety of CHIKV interventions. Alternative adaptive study designs should be used to produce more robust evidence on the therapeutic effectiveness of management strategies.

- The evaluation of the efficacy/effectiveness of therapeutic interventions during the acute phase of CHIKF depends on the definition of outcomes and how to measure what can be related to the spectrum of clinical manifestations.

- Systematic ways to evaluate and classify patients using standardized rheumatologic assessment tools are yet to be validated in different settings so they can be widely and universally adopted.

- A complete description of the drugs, information about the administration routes, duration, and safety of the treatments are lacking or are poorly described in most studies and compromises evaluation of effectiveness issue.

- Currently, there are no evidence-based treatment recommendations for the musculoskeletal disorders following CHIKV infection, making it paramount that high-quality prospective trials are conducted to fill this gap

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Reference annotations

** Of interest*

*** Of considerable interest*

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Additional file 1– Search Strategy performed in the databases.

Database	**Syntax**
Medline	((((((chikungunya virus[Title/Abstract]) OR chikungunya fever[MeSH Terms]) OR chikungunya fever[Title/Abstract])) AND (((((treat*[Title/Abstract]) OR drug therapy[Title/Abstract]) OR therapy[Title/Abstract]) OR management[Title/Abstract]) OR intervention[Title/Abstract])) AND ((adult[MeSH Terms]) OR aged[MeSH Terms])) AND humans[MeSH Terms]
Embase	('treat*':ab,ti OR 'drug therapy':ab,ti OR 'therapy':ab,ti OR 'management':ab,ti OR 'intervention':ab,ti) AND ('adults'/exp OR 'aged'/exp) AND ('human'/exp) AND ('chikungunya virus'/exp/mj OR 'chikungunya'/exp/mj)
Lilacs	tw:((tw:(chikungunya)) AND (tw:(treatment))) AND (instance:"regional") AND (fulltext:("1") AND db:("LILACS")) tw:((tw:(chikungunya fever)) AND (tw:(management))) AND (instance:"regional") AND (db:("LILACS"))
Cochrane	("chikungunya":kw or "chikungunya virus":kw (Word variations have been searched)) AND (treat*:ti,ab,kw or "drug therapy":ti,ab,kw or "therapy":ti,ab,kw or "management":ti,ab,kw or "intervention":ti,ab,kw (Word variations have been

	searched)) AND ("adult":kw or "aged":kw (Word variations have been searched)) AND ("human":kw (Word variations have been searched))
Google Scholar	Chikungunya AND Therapy Chikungunya AND Treatment

Figure 1

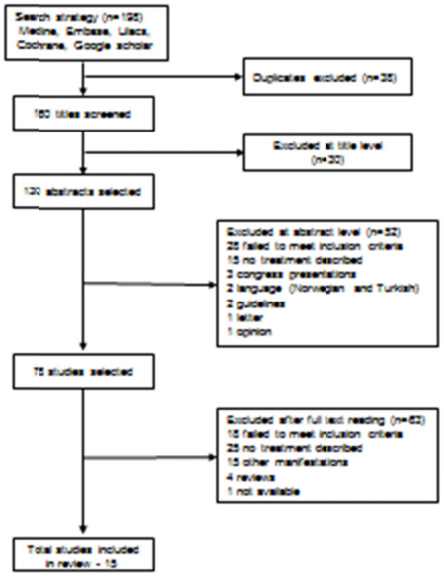

Figure 2

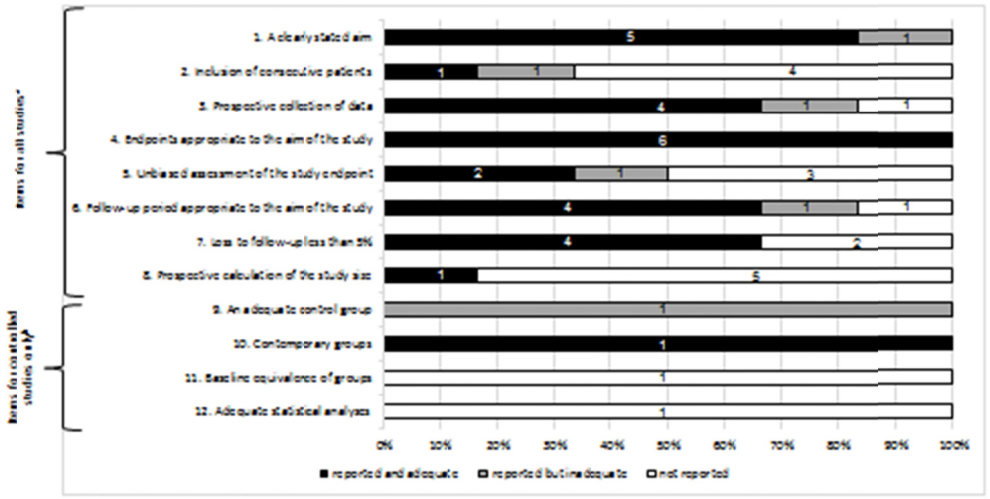

Table 1. Treatment of muscoeskeletal disorders of Chikungunya, c

Author/Year	Country	Study design	Population/Setting	Disease Onse
Simon et al , 2007 [29]	France	Observational	n=47; Female 46.8%; Outpatient Clinic and Hospital	Within 10 day More than 10 d
Ravichandran et al, 2008 [35]	India	Observational	n=20; Female 50%; Outpatient Clinic	More than 2 we
Bouquillard et al,2009 [15]	France	Observational	n=21; Female 62%; Outpatient Clinic	At least 4 mon
Malvy et al, 2009 [34]	France	Observational	n=1; Female 0%; Outpatient Clinic	1.5 year
Padmakumar et al, 2009 [13]	India	Experimental	120 (4 groups with 30 each); Female 76.7% and 80%; Outpatient Clinic	Whitin 6 weel
De Andrade et al, 2010 [37]	Reunion Island	Observational	n=106; Female 74.5%; Outpatient Clinic	At least 4 wee
Ganu and Ganu, 2011 [16]	India	Observational	n=16; Female 56.3%; Outpatient Clinic	At least 12 wee
Lui et al, 2012 [30]	Singapure	Observational	n=4; Female 50%; Outpatient Clinic and Hospital	10 days Less than 1 we 1 day 12 weeks
Chopra et al, 2014 [14]	India	Experimental	n=70 (38 and 31); Female 63.1% and 96.9%; Outpatient Clinic	At least 6 wee

Rivera-Avila, 2014 [31]	Mexico	Observational	n=1; Female 100%; Outpatient Clinic	1 day
Javelle et al, 2015 [17]	Reunion Island	Observational	n=159; Female 75%; Outpatient Clinic	More than 16 we
Peper et al, 2016 [32]	United States	Observational	n=1; Female 100%; Hospital	3 days
Redel, 2016 [36]	United States	Observational	n=1; Female 100%; Outpatient Clinic	12 weeks
Richi Alberti et al, 2016 [33]	Spain	Observational	n=4; Female 75%; Outpatient Clinic	Up to 3 week
Ravindran et al, 2017 [12]	India	Experimental	n=72; Female 65% and 69%; Outpatient Clinic	More than 1 ye

#drug classes according ATC/DDD index [36]; DMARDS= Disease Modifying Antirheumatic Drugs include the following classe
immunosuppressants, Specific antirheumatic agents, Aminoquinolines

Table 2. Treatment ef

Author	Drug	
Lui et al, 2012 [30]	Non-steroids antiinflammatory agents **AND** Coxibs **OR** Prednisolone	Clinical improvem
Peper et al, 2016 [32]	Methylprednisolone 40mg	Clinical improvem
Rivera-Avila, 2014 [31]	Metamizole soduim **AND** Paracetamol **AND** Non-steroids antiinflammatory agents	Clinical improvem
Richi Alberti et al, 2016 [33]	Non-steroids antiinflammatory agents **AND** Prednisone	Clinical improvem
Simon et al, 2007 [29]	Morphine **AND** Non-steroids antiinflammatory agents **AND** Corticosteroids **OR** Chloroquine	Clinical improvem
Author	**Drug**	
Chopra et al, 2014 [14]	Chloroquine 250 qd **OR** Meloxicam 7,5mg qd Paracetamol 500mg **SOS**	Tender joint count, joint count, VAS s score
Padmakumar et al, 2009 [13]	**GA**-aceclofenac 200mg qd **OR** **GB**-aceclofenac 200mg qd+hydroxychloroquine 400mg qd **OR** **GC**-aceclofenac 200mg qd+prednisolone 10mg qd **OR** **GD**-aceclofenac 200mgqd +hydroxychloroquine 400mg qd +prednisolone 10mg qd	VAS score ADL IADL
Ravichandran et al, 2008 [35]	Ribavirin 200mg bid	Joint involved, joint pain joint tenderness swelling
Author	**Drug**	

Bouquillard et al, 2009 [15]	Methotrexate **OR** Sulfasalazine **OR** Leflunomide **OR** Hydroxychloroquine **OR** Etanercept **OR** Adalimumab **OR** Prednisolone	Radiography (erosi radiographs)
De Andrade et al, 2010 [37]	Corticosteroids **OR** Paracetamol **OR** Destropropoxyphene **OR** Non-steroids antiinflammatory agents **OR** Paracetamol **AND** Opioids **OR** Antidepressants **OR** Antiepileptics **OR** Tramadol	VAS score, BPI, S
Ganu and Ganu, 2011 [16]	Etoricoxib 90mg qd **OR** Aceclofenac 100mg qd **AND** Prednisolone 5-10mg qd **AND** Sulfasalazine 1-2g qd + chloroquine 200mg qd **OR** Sulfasalazine 1-2g qd + chloroquine 200mg qd + methotrexate 15-20mg/week	DAS-28 score HAQ Tender joint count swollen joint count ESR
Lui et al, 2012 [30]	Non-steroids antiinflammatory agents **AND** Prednisolone	Clinical improvem
Javelle et al, 2015 [17]	Methotrexate 7,5 - 20mg/week **OR** Chloroquine 200 mg qd **OR** Non-steroids antiinflammatory agents **OR** Corticosteroids 5-40mg qd **OR** Leflunomide 10-20mg qd **OR** Sulfasalazine 1,5-3g qd **OR** Rituximab 1000mg qd **OR** Tocilizumab 8mg/kg **OR** Etanercept 25mg/2x week **OR** Infliximab 3-5mg/kg **OR** Adalimumab 40 mg **OR** Golimumab 50mg/month **OR** Abatacept 500-1000mg	Joint deformation (reported), clinical e
Malvy et al, 2009 [34]	Methotrexate 17,5mg/week	Immunological eva MRI joints (imagin
Ravindran et al, 2017 [12]	Methrotexate 15mg qd + sulfassalazine 1g qd + hidroxichloroquine 400mg qd+ prednisolone 7,5mg qd **OR** Hidroxichloroquine 400mg qd + prednisolone 7,5mg qd	DAS28, ESR, EUL
Redel, 2016 [36]	Celecoxib **AND** Colchicine 0,6-1.2 mg qd	Clinical improvem

Simon et al, 2007 [29]	Morphine **OR** Non-steroids antiinflammatory agents **OR** Chloroquine **OR** Corticosteroids **OR**	Clinical improvem

*Time of the onset of symptoms
NSAID: Non-steroids antiinflammatory agents ;DMARDs: Disease-modifying antirheumatic drug; HCQ: hydroxychloroquine; S
RA: Rheumatoid arhtritis; VAS score: Visual Analog Scale for pain; ADL: 20-point modified Barthel Index for Activities of Dail
Questionnaire; DAS-28: Disease Activity Score; MRI: Magnetic Ressonance Imaging; EULAR: European League Against Rheu