

Chikungunya virus: a rheumatologist's perspective

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ABSTRACT

Chikungunya virus (CHIKV) is an arthropod-borne alphavirus, transmitted by Aedes aegypti and Aedes albopictus mosquitoes. It is responsible for a febrile illness, typically accompanied by maculopapular rash and severe, incapacitating arthralgia. The disease, although generally self-limiting, frequently evolves into a long-lasting, debilitating rheumatic disorder, which shares many clinical features with rheumatoid arthritis (RA). The underlying mechanism by which CHIKV induces persistent arthritis remains under investigation, however, currently, attention is drawn to the fact, that chronic chikungunya (CHIK) and RA have many common cellular and cytokine pathways involved in their pathogenesis. Over the past decades, the virus has dispersed unexpectedly from tropical and subtropical regions of Africa and Asia, affecting millions of people worldwide. No licensed vaccine, nor antiviral drug against CHIKV is yet available. Treatment of acute CHIK is symptomatic, whereas in chronic stages, different disease-modifying anti-rheumatic drugs (DMARDs) have been used with variable success. Hence, chronic CHIK is an emerging rheumatic condition that rheumatologists have to deal with. This review provides brief insights into the epidemiology, pathogenesis, clinical features and management of Chikungunya disease, with special regard to post-chikungunya rheumatic disorder and its relationship with RA.

Introduction

Chikungunya virus (CHIKV) is a reemerging arthropod-borne alphavirus which causes an acute illness with characteristic, severe arthralgia. CHIKV occurrence has been primarily associated with tropical and subtropical regions of Africa, Indian Ocean islands and Asia. However, since 2005,

the virus has spread rapidly, reaching the areas with more temperate climate, including the countries in Europe and Americas (1, 2). The word “chikungunya” is derived from the Makonde language and means “that which bends up” (3). It refers to the characteristic, stooped posture that many patients develop as a result of severe joint pain they experience. In more than half of the cases, the disease leaves long-term, persistent musculoskeletal sequelae (4), which significantly affect the quality of life and, taking into account the scale of the phenomenon, may have severe socioeconomic repercussions.

The virus and the vector

CHIKV belongs to the Alphavirus genus of the *Togaviridae* family. The genus Alphavirus includes 29 recognised species, many of them being pathogenic to humans and animals. With two possible exceptions, alphaviruses are arboviruses (arthropod-borne viruses) and are therefore transmitted by infected hematophagous arthropods, chiefly mosquitoes. Alphaviruses are broadly distributed throughout the world and have been isolated from all continents except Antarctica (5). Based on their evolutionary origin, alphaviruses are commonly referred to as ‘New World’ and ‘Old World’ viruses. ‘New World’ viruses are primarily associated with potentially fatal, encephalitic disease. By contrast, the ‘Old World’ viruses, such as chikungunya, Mayaro, Ross River, Sindbis and o’nyong-nyong viruses, are responsible mostly for acute febrile illnesses followed by severe polyarthralgia (6).

CHIKV is an enveloped, positive sense, single-stranded RNA virus. Its genome of approximately 11 kb encodes four non-structural proteins and five structural proteins, including the capsid and two envelope glycoproteins, E1 and E2 (7). Genetic analysis of the E1 envelope glycoprotein sequences showed three

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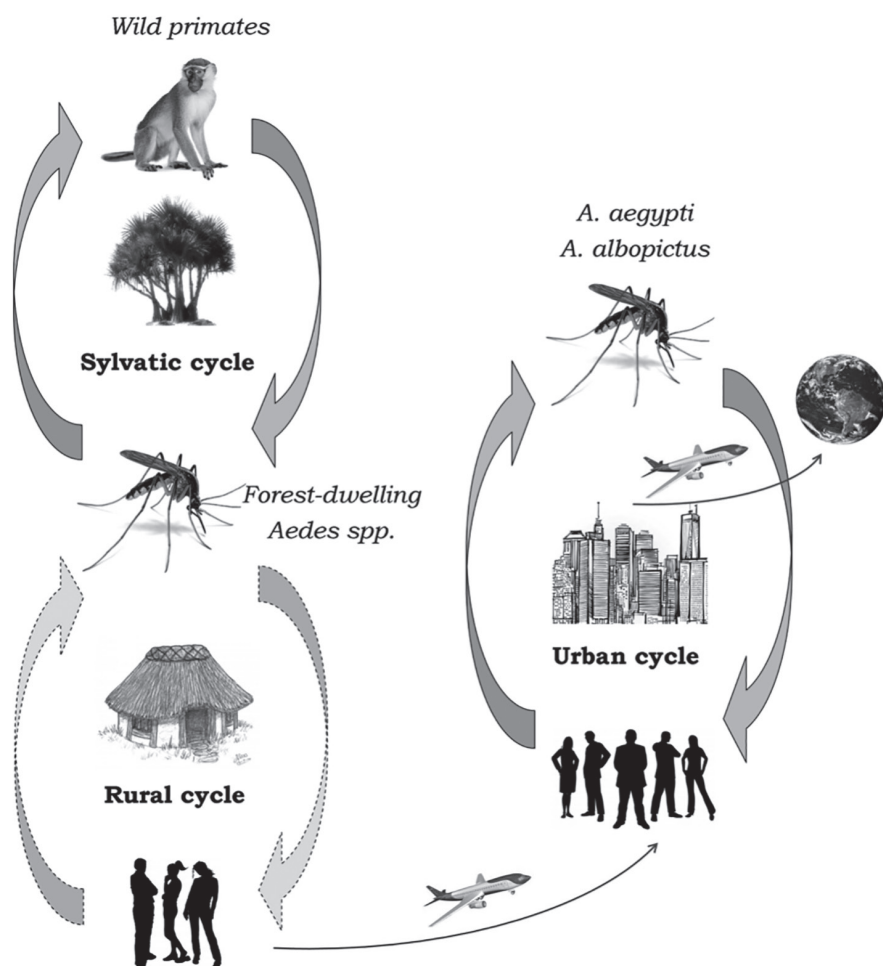


Fig. 1. Transmission cycles of chikungunya virus (CHIKV). CHIKV is typically maintained in 2 principal transmission cycles: sylvatic cycle in Africa and urban cycle (mainly in Asia). Occasionally, small human epidemics occur in rural Africa, as a spillover from sylvatic cycle. Nowadays, CHIKV can be further spread by infected air travelers and introduced to another regions populated by the epidemic vectors.

distinct lineages of CHIKV: Asian, West African and East/Central/South African (ECSA). Subsequently, the new Indian Ocean (IOL) lineage was identified from the ESCA phylogroup (8, 9). The CHIKV strains, represented in different geographic lineages, tend to circulate in different ecological cycles. In Africa, CHIKV is primarily maintained in a sylvatic cycle involving forest-dwelling *Aedes* spp. mosquitoes (e.g. *A. furcifer*, *A. africanus*) and wild primates as a reservoir hosts, being sporadically responsible for small human outbreaks in rural areas (10-12). In Asia, CHIKV typically circulates in an urban cycle between the peridomestic *A. aegypti* and *A. albopictus* mosquitoes and human hosts, with tendency to trigger large-scale epidemics over the course of several years. However, it was evidenced that also African strains

are capable of urban transmission. A schematic description of CHIKV transmission cycles is presented in Figure 1. CHIKV epidemics in Africa and Asia have been primarily associated with urban mosquito *A. aegypti*. However, since the outbreak on Reunion Island in 2005, another mosquito, *A. albopictus*, has been introduced as second major vector of CHIKV. The enhanced infectivity and transmission by *A. albopictus* was directly associated with appearance of a single mutation in the envelope E1 protein gene (A226V E1) on a ESCA-CHIKV strain (13). This adaptation was crucial for further spread of the virus, owing to the fact that *A. albopictus* is more widely distributed and has the ability to survive in temperate climates, unlike *A. aegypti*, which colonise predominantly the tropical and subtropical areas (14, 15).

Epidemiology

CHIKV was isolated for the first time in 1953, during an epidemic in Eastern Africa (present-day Tanzania) (16). Since then, the virus has been associated with several outbreaks, localised mainly in tropical and subtropical regions of Africa and Southeast Asia (17). In 2004, a large chikungunya (CHIK) outbreak occurred in Kenya, spreading rapidly between 2005 and 2006 to the Indian Ocean islands and, subsequently, to the Indian subcontinent, causing an epidemic of an unprecedented scale. About 34% of the population in Reunion Island (14) and over 1.3 million people in India (18) were affected that time. Simultaneously, numerous imported cases were reported among travellers returning from epidemic areas to Europe and United States (19-21). Owing to the fact that in some of these countries *Aedes albopictus*, a vector of CHIKV, had been already widespread, a concern about the possibility of the outbreaks in regions with more temperate climate, was born out. Indeed, a large outbreak of CHIKV occurred in 2007 in Italy (1), while cases of autochthonous chikungunya fever were recorded in France (22). Since 2006, the disease reemerged widely in Southern and Southeast Asia and spread further to Pacific Islands (17, 23, 24). Since 2013, a local transmission of CHIKV has been also identified in numerous countries or territories of the Caribbean and South, Central and North Americas (2, 25-27). For better illustration of the current epidemiologic situation, a map of CHIKV geographical distribution is presented in Figure 2.

Symptoms

Depending on the duration of symptoms, CHIKV infection may be divided into acute (the first 3 weeks from onset), post-acute (from 21st day to the end of 3rd month) and chronic stage (after 3 months from onset). The post-acute and chronic stages are observed only in a certain subset of patients (29). About 5-25% CHIKV infections are asymptomatic (30).

The incubation period for CHIKV ranges between 1 and 12 days (average 2-4 days) (31). The symptoms begin

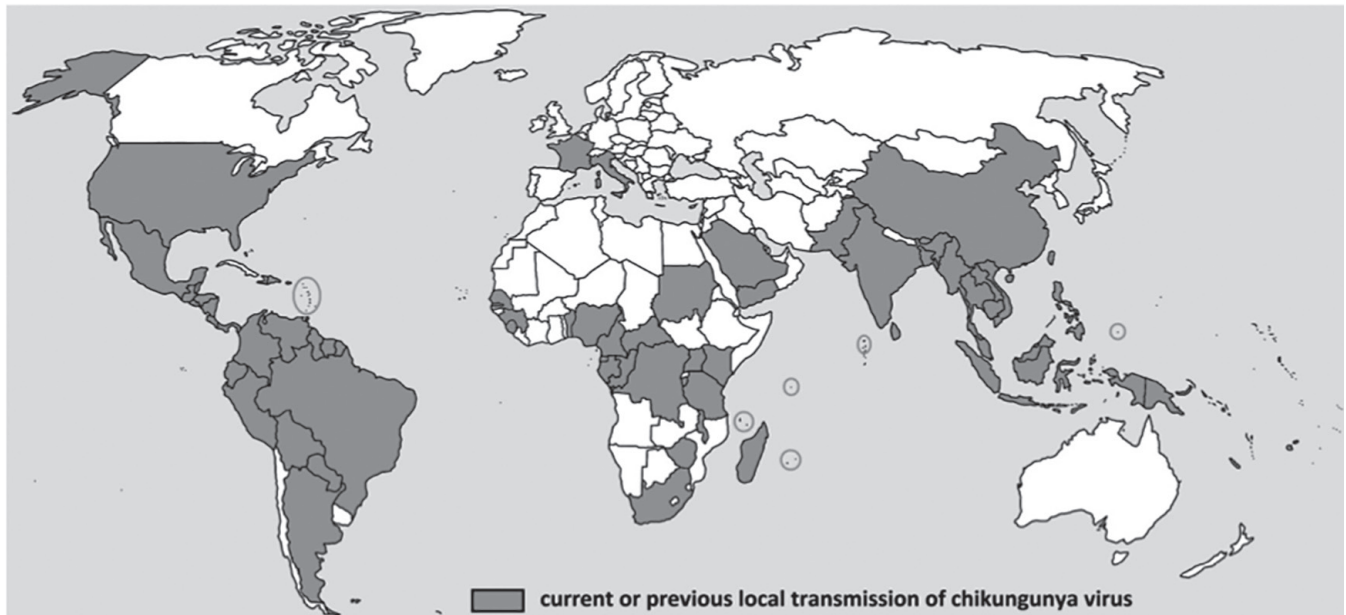


Fig. 2. A map of countries and territories where chikungunya cases have been reported (as of April 22, 2016), according to Centers for Disease Control and Prevention (CDC) (28).

abruptly, with classically reported triad of high fever, arthralgia and rash. Joint pain (typically symmetrical) occurs in up to 100% patients in acute phase and may be accompanied by their stiffness (91%) and swelling (70%). The most frequent locations of rheumatic symptoms include ankles, wrists, toes, fingers and knees. Polyarthritides (>4 joints affected) is reported in 76% of the patients (32). About 50–75% of patients develop maculopapular rash (1, 33), often with concomitant itching. The exanthema is usually transient and involves predominantly the trunk and extremities, but in some cases also the face, palms, or soles (33). Other, non-specific clinical features include generalised myalgia (79%), back pain (67%), headache (62%) and severe fatigue (37%) (3, 34). Some patients also present with photophobia and conjunctivitis (1). Gastrointestinal symptoms, such as nausea, vomiting, diarrhoea or abdominal pain, are not uncommon (20, 35), whereas, unlike dengue fever, haemorrhagic complications in chikungunya are rare (35). Neurological (*i.e.* encephalitis, meningoencephalitis, seizures, Guillain-Barré syndrome), cardiovascular (*i.e.* heart failure, arrhythmias, myocarditis, pericarditis) and respiratory (pneumonia, respiratory failure) manifestations have been also

reported and have been associated with severe course of disease (36). The overall CHIK mortality rate is low (about 0.1%), but in atypical cases it reaches almost 11% (36, 37). Atypical or severe course of the disease has been associated with several risk factors such as: concomitant respiratory or cardiologic conditions, alcohol abuse and older age (36).

The perinatal mother-to-child transmissions have been reported, with high rate of haemorrhagic, cardiac, and neurologic neonatal complications (38). Fifty per cent of neonates, born the day before to 5 days after the mother's first symptoms, become infected, usually with typical presentation of fever, difficulty in breast-feeding and pain (29). The characteristic feature of CHIK in infants is wide range of dermatological manifestations, including generalised erythema, maculopapular rash, vesiculobullous lesions and skin peeling. Other, distinctive symptoms are: febrile seizures, peripheral cyanosis and loose stools (39).

Persistent musculoskeletal symptoms were reported in 54–79% of CHIKV-infected patients 15–36 months after infection (31, 32, 40, 41). Long-term arthralgia, the most common chronic manifestation, is usually symmetrical and polyarticular (40, 41). Fingers,

wrists, knees, ankles, and toes are the most frequently affected areas during the chronic phase (40, 42). The majority of patients define the pain as intermittent, however, in 35% of cases it has permanent character (31). It may be accompanied by other symptoms such as local swelling (16–63%), morning stiffness (71–89%), fatigue (93%) and asthenia (77–85%) (31, 40, 41). The spectrum of post-CHIK musculoskeletal disease is broad and includes also tenosynovitis, plantar fasciitis or tunnel syndromes (43). The persistence and intensity of symptoms often impacts the quality of everyday life, which leads to reduction of daily activities, job invalidity and depression (41, 43).

Diagnosis

The diagnosis of CHIK is based on clinical, epidemiological and laboratory criteria. The combination of high fever and severe arthralgia in conjunction with epidemiologic criteria of residing in or having recently returned from endemic areas has a high predictive value and is usually sufficient to make a diagnosis. However, CHIKV infection may be definitely confirmed only by laboratory methods, which are mandatory in any atypical or severe manifestation, or in cases of difficult differential diagnosis (44). The laboratory confirmation

can be obtained by two principal methods, namely by the detection of viral RNA or by the identification of the specific anti-CHIKV antibodies. CHIKV-RNA is detectable in plasma during the first week (4–7 days) of illness, typically with very high levels of viraemia (19, 45, 46). In this acute phase, diagnosis usually relies on detection of viral RNA in the serum through reverse transcription-polymerase chain reactions (RT-PCR). The virus can be also isolated and cultured in different cell lines (*i.e.* Vero, C6/36), however, this method is not routinely performed and it is dedicated mainly for research and epidemiological studies (9, 21).

In the later stage of infection (>5 days post onset), the sensitivity of molecular methods decreases, as a consequence of a robust immune response and corresponding reduction in viral load. Therefore, detection of anti-CHIKV IgM by immunofluorescence or enzyme-linked immune-assay (ELISA) is more valuable diagnostic test during this phase (45, 47). IgM antibodies are usually detectable on average 5th day after disease onset and disappear over a period of several weeks to 3 months. IgG response becomes detectable few days after IgM (7–10 days post onset) and may persist for years (29, 38). Four-fold increase in IgG values in samples collected at least three weeks apart also confirms the diagnosis (3).

The non-specific laboratory abnormalities, observed during an early stage of disease include: leukopenia with lymphopenia, thrombocytopenia or elevated aminotransferase levels (20). Inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), can be elevated both in acute and chronic stages (42, 48–50).

In patients with febrile illness who returned from endemic regions, not only CHIK, but also other arboviral infections, such as dengue or Zika, should be considered, as they have common clinical features and geographic distribution. Moreover, the co-infections of these viruses have been reported (35, 51–54). Other causative agents that should be taken into consideration in differential diagnosis include: malaria, leptospirosis, rickettsia, group A strep-

tococcus/rheumatic fever and a wide spectrum of viral infections, *e.g.* other alphaviruses, parvovirus B19, Epstein-Barr virus, hepatitis A, B or C virus, retroviruses, rubella or coxackie virus infection (55–57).

Pathogenesis of chronic arthralgia

After inoculation through the bite of an infected mosquito, CHIKV enters directly the subcutaneous capillaries, infecting susceptible cells in the skin, such as macrophages, fibroblasts or endothelial cells. Then, free virions and infected cells disseminate through the bloodstream in the host organism to the peripheral organs such as liver, spleen, muscles and joints, where further viral replication occurs (7, 58, 59). CHIKV infection triggers rapid innate immune responses, primarily by strong activation of type 1 interferon (IFN) and by production of proinflammatory cytokines (7, 60). Afterwards, the adaptive immune response begins to be stimulated, with production of specific IgM and IgG antibodies (61–63).

Despite a robust innate and adaptive immune response during an acute phase, which results in viral clearance from blood, a substantial proportion of patients experience long-lasting, persistent joint symptoms. The underlying mechanism by which CHIKV induces chronic arthritis remains under investigation. At least three theories explaining this phenomenon have been proposed: 1) persistence of the infectious virus; 2) persistence of viral nucleic acids which induce persistent immunopathology; 3) triggering of persistent immune activation in certain individuals after the infectious virus has been cleared (64). It is assumed that virus may 'hijack' and replicate in synovial macrophages, as CHIKV-RNA was isolated from synovial tissue of symptomatic patients several months post infection (46). The role of macrophages in CHIKV infection is dual: they are involved in viral clearance but, on the other hand, they are also important targets for virus infection themselves (7, 65). Persistent viral replication in synovial tissue may lead to sustained inflammatory response in several probable mechanisms, *e.g.* by release of

proinflammatory cytokines, by disturbing the Th1/Th2 balance in favour of proinflammatory Th1 cells, or by inducing apoptosis of infected cells (7). Currently attention is drawn to the fact, that chronic CHIK and RA have many common cellular and immune mediators involved in their pathogenesis (49, 65, 66). Another parallels relate to their influence on bone homeostasis. The healthy bone structure is maintained by the balance between bone-resorbing osteoclasts and bone-forming osteoblasts. The process of osteoclasts differentiation depends on the interaction between pro-osteoclastogenic cytokine RANKL [receptor activator of nuclear factor (NF)-κB ligand] and its receptor, RANK, localised on the surface of osteoclasts precursors. This interaction can be inhibited by osteoprotegerin (OPG), decoy receptor for RANKL. In RA, the RANKL:OPG ratio is increased upon joint inflammation, which promotes bone resorption and contributes to the occurrence of arthritis/arthralgia. Recent studies showed that replication of the CHIKV in joint tissue can induce expression of the osteoclastogenic cytokines, such as IL-6 and RANKL, and therefore also disrupt the RANKL:OPG ratio (7, 67, 68). Taking the above into account, it is not surprising that radiographic evidences of bone erosions similar to RA have been reported in CHIKV-infected patients (43, 50).

A new prospect in the understanding of arthritic manifestations mechanisms has been opened by Reddy *et al.*, who identified structural homology between CHIKV glycoprotein and two human host tissue proteins. Moreover, the injection of this CHIKV peptides into mice induced significant muscle inflammation. Based on their experiment, the authors conclude that molecular mimicry may be involved in development of post-CHIK rheumatic disorders (69). Another argument in favour of molecular mimicry hypothesis is that CHIKV has been pointed as one of the microbial agents most likely to interact with HLA-DR, the strongest genetic determinant of RA (66). However, the hypothesis that CHIKV can trigger autoimmune reactivity in rheumatoid arthritis needs to be verified.

Risk factors for chronic arthralgia

Several studies focused on identification of the factors associated with increased risk of progression to post-CHIK chronic disease. Older age (>35–60 years) was one of the most frequently mentioned predictors of non-recovery (31, 32, 41, 46). Another identified risk factors included: female gender and baseline symmetrical distribution of joint symptoms (31), initial severe joint pain and pre-existing osteoarthritis comorbidity (32), high DAS-28 and WHODAS-II scores at diagnosis (42), and high viral loads during the acute phase (46). Among inflammatory biomarkers, high levels of interleukin-6 (IL-6) (42) and hyperferritinaemia were (70) found to be related to the severity and chronicity of joint involvement.

The spectrum of post-chikungunya rheumatic disorders

The clinical spectrum of post-CHIK rheumatic disorders is very wide, and although long-term arthralgia is considered the most frequent manifestation of chronic disease (41), a certain proportion of patients present also with symptoms of inflammation, such as arthritis, enthesitis, tenosynovitis or inflammatory joint pain (29, 71). They can be categorised into three distinct groups: rheumatoid arthritis (RA), spondyloarthritis (SA) and undifferentiated polyarthritis (UP). The diagnostic criteria for RA and SA are strictly defined, while UP has neither clinical, nor radiological specific features, and diagnosis is based on exclusion of other rheumatisms. RA is considered the most common presentation of post-CHIK chronic inflammatory disease (29, 43). Among SA, the most frequently observed pattern is psoriatic or pseudo-psoriatic polyarthritis (34, 43, 71). Interestingly, the positivity status of HLA-B27 is significantly lower in post-CHIK SA, as compared to other spondyloarthropathies (43).

The association between CHIKV and RA remains ambiguous. There are only few studies investigating the RA incidence in patients diagnosed with CHIK. Based on them, about 5–36% of symptomatic patients meet the ACR criteria for rheumatoid arthritis 10–27 months

after infection (31, 48). As regards the serological findings, there are substantial differences in estimated prevalence of rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) positivity in post-CHIK rheumatic disorders. For example, Javelle *et al.* reported the 30% prevalence of RF/ACPA positivity (43), while Manimunda *et al.* reported only 5% positivity rate for ACPA and 100% negativity rate for RF (48). Bouquillard identified 21 patients, who met ACR criteria of post-CHIK RA: 57% of them was positive for RF and 29% was positive for ACPA. Despite the low rate of ACPA, the course of disease was severe in most cases (50). Interestingly, RF may be found positive during acute stage of disease and persist positive in chronic cases or become negative in resolved cases (42). Bone erosions, a radiographic hallmark of RA, have been also reported in post-CHIK arthritis. In two studies, radiographic evidence of joint damage was seen in about 80% of patients with post-CHIK RA (43, 50). However, large-scale studies need to be prepared to assess the long-term bone structure consequences of CHIKV infection.

Treatment

To date, neither specific antiviral drug, nor effective vaccine against CHIKV infection has been registered. In acute stage, the treatment is mainly supportive and consists of fluids, analgesics and antipyretics. Paracetamol is the preferred and usually sufficient drug to control the fever and pain (3), however, some cases may require using opioids from second, or even third step of the analgesic ladder (29, 72). Non-steroidal anti-inflammatory drugs (NSAIDs) are not recommended due to increased risk of bleeding and, as for aspirin, the possibility of Reye's syndrome development. Corticosteroids should also be avoided in acute viral stage because of their impairment in natural recovery process and because of the rebound effect after discontinuation (55).

In the chronic stage, the treatment consists of medications developed for other rheumatic disorders, mainly: NSAIDs, corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs). Dif-

ferent DMARDs, such as methotrexate (MTX), sulfasalazine (SSZ), chloroquine (CQ) or hydroxychloroquine (HCQ), have been used in treatment of post-CHIK arthritides (34, 50, 71, 73, 74). However, little evidence of their efficacy is available from large clinical trials. CQ and HCQ are readily prescribed drugs, nevertheless, in a randomised study conducted by Chopra *et al.*, CQ showed no advantage over meloxicam in treatment of early musculoskeletal pain and arthritis (75). Recently, Ravindran *et al.* (76) showed the results of the first randomised controlled study evaluating the combination DMARDs therapy in chronic persistent CHIK. Seventy-two patients who were already taking HCQ and had active arthritis, were randomised into two groups: triple therapy of MTX (15mg/week), SSZ (1g/day) and HCQ (400mg/day) compared to continuation of HCQ 400 mg/day monotherapy. The authors found that a triple combination therapy was superior to HCQ monotherapy, with higher percentage of patients achieving EULAR good clinical response (85% vs. 14%) and low disease activity (54% vs. 0%) after 24 weeks of treatment. However, in either group none of the patients achieved remission (DAS 28 ESR <2.6). Hence, to achieve better outcomes in clinical practice, the authors suggest using higher doses of MTX and SSZ. As for biologic agents, there are only single reports of their application in post-CHIK RA (50). However, taking into account a significant overlap in different inflammatory pathways associated with CHIKV arthritis and RA, there is an expectancy that biologic agents developed for RA might also be effective in alphaviral arthritides therapy (77). Recently, Miner *et al.* (78) examined the efficacy of several DMARDs in CHIKV arthritis, showing that abatacept (a T-cell co-stimulation modulator) and tofacitinib (the Janus kinase inhibitor) ameliorate acute joint symptoms in mouse models. Moreover, a combined therapy of abatacept and an anti-CHIKV human monoclonal antibody provided both clinical improvement and decrease of many measured chemokines. Therefore, authors suggest that such combination of antiviral

and immunomodulatory therapy may be also beneficial in humans. It is also suggested that elevated profiles of pro-inflammatory factors such as TNF- α , INF γ , CCL-2, IL-6 or IL-17 not only play a crucial role in alphaviral joint pathology, but should also be considered as potential therapeutic target (79). Since it was demonstrated that CHIKV-specific CD4⁺ T cells are important mediators of inflammation in virus-induced joint pathology (80), recently Teo *et al.* assessed the efficacy of a few clinically approved T cell suppressive drugs in CHIKV-infected mice (81). The administration of fingolimod, an agonist of the sphingosine 1-phosphate receptor, alleviated acute joint inflammation by limiting cellular infiltration of pathogenic CD4⁺ T cells. However, further studies on the effectiveness of this drug in chronic CHIK are required. Due to the paucity of large-scale clinical trials evaluating effectiveness of different therapies in patients with chronic CHIK, the broadly accepted consensus regarding its management has not been established yet. Nevertheless, it seems reasonable to adjust the treatment of chronic CHIK to its clinical manifestation, especially to the presence or the absence of inflammatory symptoms (43). Recently published French (29) and Brazilian (82) guidelines may provide an aid in choosing appropriate drug for different types of post-CHIK rheumatic disorders.

In recent years, several candidate vaccines have undergone the first phase of clinical trials in humans, however, further studies are needed on a larger and more diverse population, to prove their efficacy (83, 84). To date, the only available method of prevention is avoidance of mosquito bites (repellents, mosquito nets, appropriate clothing). Persons infected with CHIKV should be protected from mosquitoes during the first week of illness to prevent further viral spread (2).

Conclusions

Currently, in the era of globalisation and increased international travel, and due to widespread distribution of the mosquito vector, *Aedes albopictus*, CHIKV is becoming a substantial threat to human health worldwide, including the

industrialised countries of temperate climate. Given the lack of effective vaccine or antiviral drug, the long-term consequences of infection appear to be even more deleterious. Hence, rheumatologists need to be prepared for management of this emerging rheumatic condition and should consider CHIKV as possible cause of persistent arthritis/arthritis in patients residing in or having recently returned from endemic areas. There is undeniably a wide range of clinical and pathogenic affinities between CHIK arthritis and RA, however, further studies are necessary to provide a better understanding of these associations.

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