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REVIEW

Chikungunya Arthritis

Implications of Acute and Chronic Inflammation Mechanisms on Disease Management

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In the past decade, arboviruses—arthropod-borne viruses—have been the focus of public health institutions worldwide following a spate of devastating outbreaks. Chikungunya virus, an arbovirus that belongs to the alphavirus genus, is a reemerging arthritogenic virus that has caused explosive outbreaks since 2006, notably on Réunion Island, and more recently in the Caribbean, South America, India, and Southeast Asia. The severity of arthritic disease caused by chikungunya virus has prompted public health authorities in affected countries to develop specific guidelines to tackle this pathogen. Chikungunya virus disease manifests first as an acute stage of severe joint inflammation and febrile illness, which later progresses to a chronic stage, during which patients may experience debilitating and persisting articular pain for extended periods. This review aims to provide a broad perspective on current knowledge of chikungunya virus pathogenesis by identifying key clinical and experimental studies that have contributed to our understanding of chikungunya virus to date. In addition, the review explores the practical aspects of treatment and management of both acute and chronic chikungunya virus based on clinical experience during chikungunya virus outbreaks. Finally, recent findings on potential therapeutic solutions—from antiviral agents to immunomodulators—are reviewed to provide both viral immunologists and clinical rheumatologists with a balanced perspective on the nature of a reemerging arboviral disease of significant public health concern, and insight into future therapeutic approaches to better address the treatment and management of chikungunya virus.

Introduction

Arthropod-borne viral infections have recently dominated the headlines following a spate of significant outbreaks around the world. Mosquito-borne viruses such as chikungunya virus have sparked the attention of global health organizations and led to robust public health interventions. Outbreaks of chikungunya virus had been reported in Africa, Asia, and the Indian and Pacific Oceans since the mid-2000s; a small number of cases have also been reported within Europe (1,2). In 2013 the chikungunya virus epidemic reached the Americas and it is now spreading through South America, with >1 million cases reported (3–5). In the US, travel-associated cases have been reported in 37 states (1) within the mainland US (as of January 2017), with cases of local transmission also reported in Florida (2). Of more pressing concern, India (3) and most Southeast Asian countries have been subjected to unabated epidemics that have proven difficult to control. Propitious climate, facilitated by seasonal monsoons and urban areas where mosquito vector control is lacking, along with a reservoir of naive populations, are major contributing factors to the risk posed by locally acquired chikungunya virus infections in developing countries (4). While developed economies that have experienced significant numbers of traveler-imported cases are

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somewhat equipped to manage the chikungunya virus disease burden, less economically developed regions of the world—in particular densely populated urban areas—where epidemics have become most resilient have seen their public health systems overwhelmed by the disease (3,5).

Chikungunya virus symptoms include a range of acute manifestations, among which fever, severe joint and muscle pain, headache, and rashes are prominent. However, there is mounting concern over the persistence of long-lasting manifestations associated with debilitating effects of the disease and the deterioration of overall health and quality of life (6–9). Among these, chronic arthralgia/arthritis (joint pain/joint stiffness plus joint swelling, respectively), musculoskeletal injury, and fatigue—and, to a lesser extent, neurocognitive and sensorineural manifestations—have been shown to contribute significantly to the economic burden of the disease (10,11). Although vaccines have reached human trials (12,13) and a range of potential antiviral compounds have undergone preclinical evaluation (14,15), no licensed vaccines or antiviral therapies are available. Both acute and chronic disease manifestations are of significant concern, and there are currently no specific, approved drugs to treat either form of the disease. Chronic chikungunya virus poses important questions with regard to public health policy and interventions. Should efforts be directed at managing the early stages of the disease, to limit the consequences on population productivity and lessen the burden of a "patient rush" on often-under equipped hospitals, or should more attention be focused on limiting the development of chronic disease, associated with persistent rheumatic disease and a risk of long-term impact on population health?

In this review, we address the key pathophysiologic mechanisms that drive acute and chronic chikungunya arthritis, arguably the most incapacitating phenotype among long-lasting chikungunya virus disease manifestations, based on recent animal experimental disease models and epidemiologic studies. We explore the latest findings in therapeutic development aimed at both limiting viral spread and at immune and inflammatory mechanisms, and address the implications of such findings in current and future clinical care of chikungunya virus patients.

Chikungunya virus is recognized as an emerging biphasic disease, described as an acute infection followed by persistent symptoms. Hence, experts have defined 3 successive clinical stages, taking into account known difficulties in practical management. In symptomatic, infected individuals, the first stage encompasses an acute incapacitating febrile viremic phase together with residual symptoms. The 2 final stages are characterized by persistent manifestations: a post-acute stage (from 21 days after the onset of infection to the end of the third month) and a chronic stage (beyond 3 months). Schematically, the disease progresses to resolution without sequelae either spontaneously or after treatment, or to a persistence of articular and general symptoms, or to aggravation due to an inflammatory or degenerative process.

Acute and post-acute stages of chikungunya virus (≤3 months after the onset of infection)

After a silent incubation of 4–7 days, the acute stage of chikungunya virus disease can be divided into 2 distinct phases, the viremic phase (5–10 days) and the post-viremic phase (6–21 days) (16–18). In the most common manifestations, the viremic phase is marked by unusually high-grade fever (>39°C) with abrupt onset, accompanied by severe incapacitating oligo- or polyarthralgia/arthritis (<4 or ≥4 joints, respectively, with debilitating and sudden injury), myalgia, headache, backache, and cutaneous rash, whereas the post-viremic phase is characterized by apyrexia (no fever), polyarthralgia/arthritis, and to a lesser extent, myalgia, pruritus, fatigue, and lymphadenopathies and anorexia, though the latter are less common (18). Joint pain is most often symmetric and additive and affects the large and smaller articulations of both the arms (most commonly the wrists, followed by the phalanges, shoulders, and elbows) and the legs (most commonly the ankles, followed by the knees, feet, and hips). Atypical locations include vertebral, temporomandibular, or sternoclavicular articulations (17). Stiffness and swelling, indicative of synovitis, are observed in the ankles, phalanges, wrists, and toes, but very exceptionally in larger joints (17). After infection, IgM antibody isotype appears within days of the onset of symptoms, and neutralizing anti–chikungunya virus IgG typically appears by the second week (19).

Acute chikungunya virus infection (<21 days after the onset of infection) is consistently associated with a strong host antiviral type I interferon (IFN) response. RNA sequencing (RNASeq) analysis of acute chikungunya virus infection in a mouse model revealed that approximately half of all genes up-regulated after infection are IFN-stimulated genes (ISGs) (20,21). IFNα is detected early in infection, reaching levels of 700 pg/ml in the plasma of chikungunya virus–infected patients, coinciding with the onset of disease symptoms (16,22). During the acute stage, patient viremia has been shown to directly correlate with production of cytokines such as IFNα and interleukin-6 (IL-6) (20,22). Although this correlation is lacking in other studies, it is broadly accepted that all patients experiencing acute chikungunya virus infection

produce high levels of IFNα (20). This is also observed in animal models of acute chikungunya virus disease (21,23–25). Indeed, chikungunya virus infection is generally fatal in mice deficient in type I IFN responses, while arthritogenic manifestations are exacerbated in IFNα/β-deficient mice infected with chikungunya virus (24–26). Furthermore, downstream effectors of IFN induction such as ISGs play key roles in inhibiting chikungunya virus infection (21), and a strong IFN response is associated with a milder course of disease in mice infected with alphaviruses (24,25,27). The ability of alphaviruses to develop mechanisms to inhibit host IFN induction and signaling (28) also highlights the importance of this early innate immune response in controlling infection (29).

In addition to a potent type I IFN response, the acute stage of chikungunya virus infection (<21 days after the onset of infection) is associated with elevated patient plasma levels of multiple soluble factors, including proinflammatory cytokines and chemokines (CCL2, macrophage migration inhibitory factor, CCL4, CXCL10, IL-6, IL-8, and IL-16), antiinflammatory cytokines (IL-1 receptor A, IL-10, and IL-13), growth factors (granulocyte colony-stimulating factor [G-CSF], granulocyte–macrophage colony-stimulating factor [GM-CSF], vascular endothelial growth factor, and stem cell growth factor β) and other mediators (IFNγ, IL-4, IL-7, and CXCL9) (20–22,30–33). This results in intense monocyte trafficking to the infected tissues (33), along with strong activation of both CD8+ T and natural killer (NK) cells to assist in clearing the virus (20,34). The post-acute stage of chikungunya virus (from the fourth week to the third month after the onset of infection) is characterized by very polymorphous manifestations prolonging the initial inflammatory symptoms (acute arthritis) by diverse rheumatic disorders, including periarticular involvement, slowly regressive enthesitis, tenosynovitis, and bursitis, together with nonrheumatic and systemic symptoms (18). This stage is marked by persistence of IL-6 and GM-CSF secretions and production of IL-17 in the most affected patients, or by eotaxin and hepatocyte growth factor in those who have fully recovered (20).

Chronic stage of chikungunya virus (>3 months after the onset of infection)

While 50–60% of patients with acute chikungunya virus recover fully or with mild-to-moderate sequelae, in some the disease evolves to a chronic stage that can last up to several years (18,35). Beyond the post-acute stage, chronic chikungunya virus is thus characterized by the persistence of arthritic conditions associated with long-term sequelae, such as fatigue and depression, stemming from prior rheumatic conditions, although not a prerequisite, or in the wake of an authentic arthritogenic alphaviral infection. Chronic chikungunya virus is associated with high levels of circulating IL-6 and IL-12 (22,31,36). IL-6 is specifically expressed in the affected joints and could stimulate the release of RANKL while inhibiting the action of its decoy receptor osteoprotegerin released by osteoblasts, resulting in osteoclastogenesis and severe bone loss, as has been shown in mice (37–40). Indeed, while bone loss is not a defining feature in patients with chronic chikungunya arthritis, recent studies appear to implicate IL-6 as a possible biomarker of chronic chikungunya virus (41,42).

In addition to soluble host factors responsible for regulating antiviral responses, CD4+ T cells have been shown to be a major driver of arthritic disease during chikungunya virus infection in mouse models (43,44) and in the follow-up of patients with chronic chikungunya arthritis (45). Moreover, impaired NK cell function was shown to be associated with chronic arthritis in infected patients (46). Importantly, Treg cells, a subset of CD4+ T cells, may play a role in moderating excessive chikungunya virus–induced immune responses. Treg cells compete with naive T cells to interact with antigen-presenting dendritic cells. Treg cells interacting with dendritic cells were shown to cause mature dendritic cells to down-regulate costimulatory signaling, curtailing the expansion of chikungunya virus–specific CD4+ T cells, thus effectively reducing chikungunya virus–induced joint swelling in mice (47). B cells and neutralizing antibodies, especially the IgG3 subclass, are also critical for chikungunya virus clearance (19,48). The immaturity of cellular and humoral immunity may, if only partly, explain the rarity of chronic arthralgia in children younger than 3 years of age.

The role of myeloid cells is less clear in the chronic stage of human chikungunya virus infection, where they may be involved in the clearance of infected cell debris which, when acting as a source of pathogen-associated molecular patterns, may trigger or drive chronic chikungunya virus (49). Monocytes and macrophages recruited to the sites of inflammation during chikungunya virus infection dominate the cellular infiltrates (23,33). However, in studies using mice deficient in the chemokine receptor CCR2, the monocyte/macrophage infiltrate was replaced by a severe neutrophil infiltrate, exacerbating chikungunya virus–induced inflammation and cartilage damage (50). Thus, although recruited CCR2+ monocyte/macrophages contribute to inflammation, they may also be needed to prevent excessive pathology or promote resolution of disease following chikungunya virus infection.

Interestingly, a recent RNA Seq analysis of chikungunya virus–infected mouse tissues demonstrated good concordance with the expression of genes reported to be up-regulated in chikungunya virus patients (21). Most

genes were associated with inflammation, indicating consistent proinflammatory gene expression in both mouse and non-human primate models and chikungunya virus–infected patients. This suggests that chronic chikungunya virus may represent an extension of acute disease rather than an activation of, or progression to, new inflammatory immunopathologies. Antiinflammatory treatments that effectively target acute chikungunya virus may thus also have utility in treating chronic chikungunya virus (21). Prominent in the RNA Seq analysis of chikungunya virus infection in mice was the serine protease granzyme A (21). Granzyme A was found to play a proinflammatory role in chikungunya virus in mice and was also found in the sera of chikungunya virus–infected non-human primates and in symptomatic chikungunya virus–infected patients. The mouse granzyme A inhibitor, Serpinb6b, significantly reduced foot swelling in chikungunya virus–infected mice, indicating that granzyme A may be a potential therapeutic candidate (21). Granzyme A was also recently shown to be important in a mouse model of rheumatoid arthritis (RA) (51), an example of the significant overlap between chikungunya arthritis and RA (43,45).

Chronic chikungunya arthritis and implications for therapy

Risk factors for the development of chronic chikungunya arthralgia/arthritis. Although most patients recover from acute chikungunya virus infection within days or weeks, instances of persistent post–chikungunya virus rheumatic disease—chronic and incapacitating joint morbidities—have been reported in a recent systematic review (35), and in up to 40% of patients on average in a recent meta-analysis (52). This often painful, incapacitating chronic chikungunya virus disease—of a primarily rheumatic nature, though as noted above, prior rheumatic conditions are not a prerequisite—can persist for years in some patients and is highly detrimental to their health and quality of life (6–10,36,52–63). Although there have been numerous studies focusing on acute chikungunya virus infection and potential treatments, the mechanisms that cause chikungunya virus to progress to a chronic stage are still poorly understood.

One hypothesis is that comorbidities such as preexisting joint disease (e.g., osteoarthritis or RA), metabolic syndrome features (e.g., hypertension, obesity, or diabetes mellitus), or both prior to chikungunya virus infection may exacerbate chikungunya virus–induced arthritis or increase patient susceptibility to developing chronic chikungunya virus polyarthritis (54,58,59). In the population-based TELECHIK study, preexisting rheumatic disorders and metabolic syndrome were both associated with long-lasting rheumatic pain in an unadjusted analysis (10,58). However, a separate study from Réunion Island showed that only 2.8% of the hospital-based patients who had chronic chikungunya virus had preexisting joint disease (59). Given such discrepancies across studies, any link between preexisting joint disease and an increased risk of developing chikungunya arthritis remains unproven (35,53,57,62,63). Risk factors for the development of chronic chikungunya arthralgia include an age of >45 years (54,58), severe (9,54,58) or long-lasting (9,60) acute chikungunya virus, a high viral load (>10^9/ml) during the viremic phase (36), and an intense chikungunya virus immune response in the post-viremic phase (58).

The case for viral persistence. In most viral arthritides, arthritic disease is associated with the presence or persistence of replicating virus and/or viral debris in joint tissues (64). A substantial body of evidence supports the view that the same underlying mechanism is responsible for alphaviral arthritides, including chikungunya arthritis. Poo et al reported detection of significant levels of chikungunya virus RNA in the feet of wild-type C57BL/6 mice up to 100 days after infection (65), which is consistent with studies in non-human primate models (23,66), and to date, a single clinical observation (36). Chikungunya virus proteins and continued virus-specific T cell responses were also detected throughout the chronic stage of disease in C57BL/6 mice (65) and in rhesus macaques (66). Importantly, the latter model showed that the intensity of the T cell response was age dependent, as evidenced by diminished T cell infiltrates and a more pronounced persistence of chikungunya virus in the tissues of aged monkeys (66), consistent with human pathology (54,58). Interestingly, the hierarchy of the T cell response in humans follows a shift from CD4 to CD8, which may be indicative of a role of aging in chikungunya virus immunopathology (67).

Although persistent chikungunya virus RNA has been detected in chronic disease (with double-stranded RNA by itself known to be arthritogenic [68]), investigators have been unable to isolate infectious virus from tissue or sera in mouse models and human studies (36,65). Human studies have shown high levels of chikungunya virus–specific IgM up to 180 days in patients with no preexisting musculoskeletal disease prior to infection (36,53), and even a case of severe destructive arthritis that exhibited chikungunya virus–specific IgM over 24 months (55). These findings suggest that the persistence of viral antigens could be a contributing factor to the development of chronic chikungunya arthritis, but the underlying molecular mechanisms are still unknown, and a statistical association between persistent chikungunya virus–specific IgM and chronic arthralgia has not yet been established (53). Immunohistochemical analysis revealed the presence of

chikungunya virus antigen in muscle satellite cells and perivascular macrophages in muscle and synovial tissue in patients with chronic chikungunya virus (36,69). This suggests that infection of muscle satellite cells—myogenic precursor cells responsible for postnatal muscle growth and repair—could be an underlying cause of the persistence of chikungunya virus in muscle tissues (69,70).

Clinical care of chikungunya virus patients: lessons learned from a decade of outbreaks

Current treatment of patients with acute and post-acute chikungunya virus (≤3 months after the onset of infection). The management of acute chikungunya virus involves both supportive care and physical measures, and the physician's role is important. Given the potential for corticosteroids to exacerbate viral arthritides (71), treatment with nonsteroidal antiinflammatory drugs (NSAIDs) remains a key disease management approach (72). However, to date there is no effective antiviral treatment licensed for clearing the virus. In the acute stage of chikungunya virus (≤3 weeks after the onset of infection), the therapeutic aims are first to alleviate fever and pain and then to prevent short-term (i.e., organ dysfunction due to chikungunya virus or of iatrogenic origin), post-acute, and chronic complications. In the post-acute stage (≥4 weeks after the onset of infection), the therapeutic strategy is based on a patient-centered approach, with the objectives of relieving pain and inflammation, preventing stiffness, loss of muscle tone, and loss of physical fitness, and limiting the consequences of the inflammatory process (18). At this stage, treatment primarily consists of analgesics and NSAIDs, though it must be noted that NSAID treatment depends on the clinical presentation, since no NSAID class has demonstrated a clear benefit or effectiveness for post–chikungunya virus symptoms. NSAIDs are prescribed at full dose (within critical tolerance), and their effectiveness is reassessed (with regard to dose and schedule) during the first week or within the first 10 days. If well tolerated, NSAID treatment can be extended up to several weeks before gradual weaning.

For fever and pain alleviation, acetaminophen is relied on as a first-line medication (level 1). The risk of acute hepatitis is increased in the case of severe pain (which often requires supratherapeutic doses), underlying comorbidities (alcohol use, liver diseases, or malnutrition), or drug interactions (unwanted self-medication). When acetaminophen fails, second-line treatment consists of adding weak opioids (level 2), for instance, codeine combined with acetaminophen (adult regimen contraindicated during breastfeeding), adding codeine to acetaminophen (restricted to patients age >12 years), or adding tramadol to acetaminophen (adult formulation, or pediatric formulation for children >3 years) (18). When second-line treatment fails, morphine (level 3) (extended or immediate action) can be used on a case-by-case basis, usually in the hospital, under strict monitoring and after assessment of the risk/benefit ratio due to possible side effects (respiratory, neurologic, digestive, and urinary) (18).

Corticosteroids are generally strongly discouraged, given the lack of a clear benefit in the course of severe arthritis, since it has been suggested that they may cause a rebound of arthritis or tenosynovitis (18). Notwithstanding their inherent risk, the use of corticosteroids may, in our experience, be warranted when strictly limited to highly inflammatory polyarticular injury associated with tenosynovitis or severe synovitis or when NSAID treatment has failed. Generally, a 10 mg/day course of prednisone for 5 days (with immediate de-escalation within 10 days) was found to be sufficient in moderate NSAID-refractory cases (18). As a general rule, the total duration of corticosteroid treatment must be <4 weeks, and must be followed by a switch to an NSAID to avoid deleterious clinical rebound and/or drug-induced dependence. Of note, other agents such as chloroquine have been shown to be ineffective in relieving acute pain (73) with inconclusive results regarding efficacy in relieving post-acute pain as a suboptimal cotreatment with acetaminophen (74). In the case of disease-modifying antirheumatic drugs (DMARDs), which are further discussed below, current consensus suggests no formal indication to initiate DMARD therapy before the last phase of the post-acute stage (8 weeks after the onset of infection), even with a specific antirheumatic agent such as methotrexate (MTX). Other DMARDs, such as hydroxychloroquine (HCQ), have not been shown to be effective in the treatment of post-acute chikungunya virus (75).

Systemic, cardiac, hepatic, renal, and metabolic comorbidities should be monitored closely, since some may be exacerbated by chikungunya virus or increase the severity and duration of chikungunya virus–specific arthralgia (18). Together with nonspecific routine measures used in arthritis when pain persists beyond the third week, therapeutic strategies often focus on pain management. This usually combines level 1 and level 2 analgesics with, in some cases, antineuropathic drugs (nefopam, antiepileptic, or antidepressant pain relievers) if necessary (DN4 score for neuropathic pain of ≥4) (76). As outlined above, corticosteroid treatment, either topical or via infiltration (intraarticular or intracapsular administration), should be used only for local involvement, including tenosynovitis, bursitis, capsulitis, and carpal tunnel syndrome, or synovitis that does not respond to oral treatment.

Gaps and perspectives in the treatment of acute and post-acute chikungunya virus. The intensity or duration of pain during the acute phase has been correlated with high viral loads, providing clues that viral clearance should be hastened. Ribavirin and IFNα have shown synergistic antiviral activity against chikungunya virus in vitro; however, neither of these are recommended for daily use due to the risk of side effects (77). Favipiravir (T-705), a viral RNA polymerase inhibitor licensed in Japan for the treatment of influenza, was also found to inhibit chikungunya virus replication in vitro (78) and could become the focus of studies assessing its usefulness in treating chikungunya virus. Suramin, a licensed drug for sleeping sickness, has also shown in vitro antiviral activity through multiple mechanisms and was effective against mutant chikungunya virus strains resistant to ribavirin or favipiravir (79). Curcumin, a turmeric-derived compound used as a food additive and in herbal medicine, and its derivatives exhibit similar antiviral properties through inhibition of virus cell binding in in vitro studies (80). Finally, the short peptides pimozide and 5-tetradecyloxy-2-furoic acid were found to exhibit high synergistic antiviral activity in studies using a genome-wide loss-of-function screen (81), which further reinforces the usefulness of such a broad genome-wide scale approach in chikungunya virus disease studies. Despite significant advances in the development of chikungunya virus antiviral agents and substantial mechanistic evidence of in vitro efficacy, neither of these compounds has yet been evaluated in humans infected with chikungunya virus.

Current treatment of patients with chronic chikungunya virus (>3 months after the onset of infection). The therapeutic approach to chronic chikungunya virus requires a rheumatologist and a pain specialist, as for chronic inflammatory diseases (18). It focuses on the phenotype displayed by the individual patient, including the presence or absence of inflammatory symptoms (i.e., at least 1 joint with chronic arthritis), the number of joints involved, and the level of clinical inflammatory activity (e.g., joint destruction or extraarticular involvement). Practically, 2 distinct evolving patterns of persistent chikungunya virus rheumatic disorders can be distinguished. The large majority of patients who still have pain beyond 3 months after acute infection present with varied musculoskeletal injury, primarily tendinopathies. These patients should experience substantial improvements with prolonged administration of NSAIDs (with strictly limited use of corticosteroids) in combination with local complementary therapies. In contrast, ~5% of patients will experience conditions that fulfill the criteria for chronic inflammatory diseases, primarily potentially destructive arthritis and synovitis. Little is known about the immune (or viral) mechanisms underlying the progressive form of the disease, the development of arthritis, or predictors of this outcome.

Morphologic assessment, designed to evaluate for fulfillment of current criteria for RA and spondyloarthritis (SpA), and laboratory tests are generally performed to confirm the diagnosis and screen for evidence of inflammatory or destructive mechanisms. Incidentally, RA is the most common post–chikungunya virus chronic inflammatory disease, followed by peripheral SpA. Alternatively, nondestructive arthritis that does not meet the criteria for RA or SpA is referred to as undifferentiated polyarthritis, and may be indicated after alternative causes (such as connectivitis or lupus-like syndrome) have been ruled out. Once the type of persistent chronic chikungunya virus condition has been identified, individualized treatment is proposed based on the diagnosis, functional prognosis, and the patient's condition. Treatments aim to preserve functional outcome in order to reduce psychosocial impact and improve health-related quality of life. Ideally, treatment should begin within the first month of the chronic stage (after >10 weeks of post-acute stage).

DMARDs. Chronic chikungunya arthritis shares several characteristics with RA, such as persistent debilitating arthralgia and exacerbated inflammatory response (31,36,43,45,72). Because of these parallels, chloroquine, HCQ, and DMARDs such as MTX and sulfasalazine have been evaluated in some peri-epidemic clinical trials of treatments for chronic chikungunya arthritis (74,82–85). When compared with HCQ alone, treatment with DMARDs, either alone or in combination with HCQ and corticosteroids, has resulted in reductions in joint pain, disability, and impaired activity in cohort studies of patients with chronic chikungunya arthritis (84,85). In contrast, a cohort study showed that almost all patients had progression of disease-induced bone erosion and joint space narrowing upon follow-up despite treatment with HCQ or DMARDs, and a 2-year follow-up study involving 625 patients showed that treatment of chronic chikungunya arthritis with sulfasalazine and MTX was effective (82,86). Given the conflicting outcomes of those studies, it remains unclear whether specific DMARDs are effective in treating chronic chikungunya arthritis (85).

Experts have reached a consensus, however, that MTX should be recommended as first-line treatment (18). Though the efficacy of HCQ and other DMARDs has not been established per se using randomized controlled trials, these treatments should be considered on a case-by-case basis, either as a complement to or as an alternative to MTX (18,63,84). DMARDs must be monitored for effectiveness (using the Disease Activity Score in 28 joints) and tolerance and should be stopped after a durable remission of several months has been achieved. The specialist may

then refer to national guidelines to choose the second-line drug (combination or replacement treatments or biologic agents). However, in most cases, DMARD treatment may be assessed and stopped for patients whose disease remains in remission after a complete response has been sustained for several months (up to 2 years). Physical therapy includes rest limitation, maintenance of articular amplitude and muscular tone, and lymphatic drainage (manual, using compression stockings, or using pressotherapy) (18). Its benefit depends on the extent and the intensity of joint involvement and the disease impact in terms of autonomy and quality of life. When considering second-line treatment for patients with chronic post–chikungunya inflammatory diseases that fail to respond to first-line treatment, a multidisciplinary, case-by-case approach is advised. This may include enrollment in clinical trials assessing treatments that are recommended in national/international guidelines. One option would involve a regimen switch to combination therapy with alternative DMARDs or a biologic agent, either alone or in combination with other DMARDs.

Gaps and perspectives in the treatment of chronic chikungunya virus. Chronic pain has been linked to chikungunya virus persistence in synovial macrophages as well as to IL-6 and IL-12 secretion. To the best of our knowledge, anti–IL-6 (tocilizumab), anti–IL-12/IL-23p40 (ustekinumab), and anti-CD20 (rituximab) monoclonal antibodies (mAb) have not been tested empirically in chronic chikungunya virus, whereas anti–tumor necrosis factor (etanercept) therapy has been shown to exacerbate tissue damage in a mouse model of alphaviral arthritis (87). While several approaches (biologic, prophylactic, and palliative) are being explored and characterized to manage acute and chronic chikungunya virus, the development and testing of such therapeutic solutions should be done in close consultation with rheumatologists.

Therapeutic strategies that target monocyte chemotactic proteins or CCR2, such as bindarit, which was shown to ameliorate chikungunya virus–induced arthritis and bone loss in a mouse model (88,89), might be considered promising for further evaluation in the treatment of alphaviral arthritides. Of note, treatment of RA patients with CCR2 blockers was unsuccessful (90). Interestingly, pentosan polysulfate (PPS), a glycosaminoglycan currently approved in the US for the treatment of interstitial cystitis, has undergone promising clinical trials for the treatment of noninfectious arthritis and has been shown to maintain levels of cartilage proteoglycans in experimental animal models of arthritis (91,92). In chikungunya virus–infected mice, PPS treatment decreased the level of joint swelling and reduced levels of the soluble factors CCL2, IL-6, IL-9, and G-CSF during acute inflammation (93). Although the exact mechanism of action of PPS is unclear, treatment was associated with an early increase in antiinflammatory IL-10 levels, suggesting an indirect mechanism by which inflammation is dampened (93). As part of the Australian Government Department of Health Therapeutic Goods Administration Special Access Scheme, PPS, currently in phase II clinical trials, has now been successfully used to treat 5 patients with Ross River virus–induced arthralgia that had failed to respond to current standard treatment. Ross River virus is an Australian arthritogenic alphavirus that causes viral polyarthritis with clinical manifestations (severe, incapacitating joint pain) similar to those seen in chikungunya arthritis.

More recently, targeting CD4+ T cells with clinically approved T cell–suppressive drugs, including the sphingosine 1-phosphate receptor agonist fingolimod (also known as FTY720), successfully reduced chikungunya virus–induced disease in mice by blocking lymphoid egress and subsequent migration of CD4+ T cells into the joints (94). Although the US Food and Drug Administration (FDA) approved fingolimod as a treatment for multiple sclerosis in 2010, there are currently no clinical trials to assess efficacy in chikungunya arthritis.

Neutralizing antibodies and prophylactic treatment. A number of studies have sought to characterize the neutralizing capacity of chikungunya virus–specific antibodies, the epitopes responsible for neutralization, and the mechanism of viral inhibition (95–102). Robustly neutralizing mAb to chikungunya virus bind the E2 envelope glycoprotein with conserved epitopes identified on the A and B domain. Antibodies block multiple steps in the viral life cycle, including entry and egress, by crosslinking adjacent E2 spikes of the E2 glycoprotein or impeding fusion. Importantly, these broadly neutralizing ultrapotent mAb protect against infection by multiple alphaviruses, including chikungunya virus (95–97).

Neutralizing antibodies have been tested in mouse models as treatment for persistent chikungunya virus infection. The effect of a neutralizing anti–chikungunya virus mAb on RAG-$1^{-/-}$ mice (devoid of B and T cells) with persistent chikungunya virus infection was to enable effective clearance of infectious virus in quadriceps muscle tissue and sera, although without reducing chikungunya virus RNA load in joint tissue (103). In a separate study by Poo et al, chikungunya virus viremia became undetectable in persistently infected RAG-$1^{-/-}$ and B cell–deficient μMT mice beginning 10 days and 30 days, respectively, after administration of polyclonal anti–chikungunya virus antiserum (65). However, viremia recovered to levels similar to those observed prior to administration of the antibody, indicating that effective clearance of chikungunya virus may require robust and long-lasting B and T cell responses (65).

Further, another study showed that a highly conserved amino acid on the E2 glycoprotein promoted chikungunya virus persistence in mouse joints and impaired neutralization by antibodies targeting the E2 domain. Mutation of this conserved region allowed viral clearance and enhanced neutralization, providing the structural basis for the mechanism by which chikungunya virus evades B cell–mediated clearance in chronic joint infection (98). Finally, rhesus macaques with chikungunya virus infection treated with SVIR001, a recombinant human IgG1 mAb that recognizes the E2 glycoprotein of chikungunya virus, showed more robust viral clearance and less severe joint inflammation compared with isotype-treated controls (99). In addition, SVIR001 reduced viral

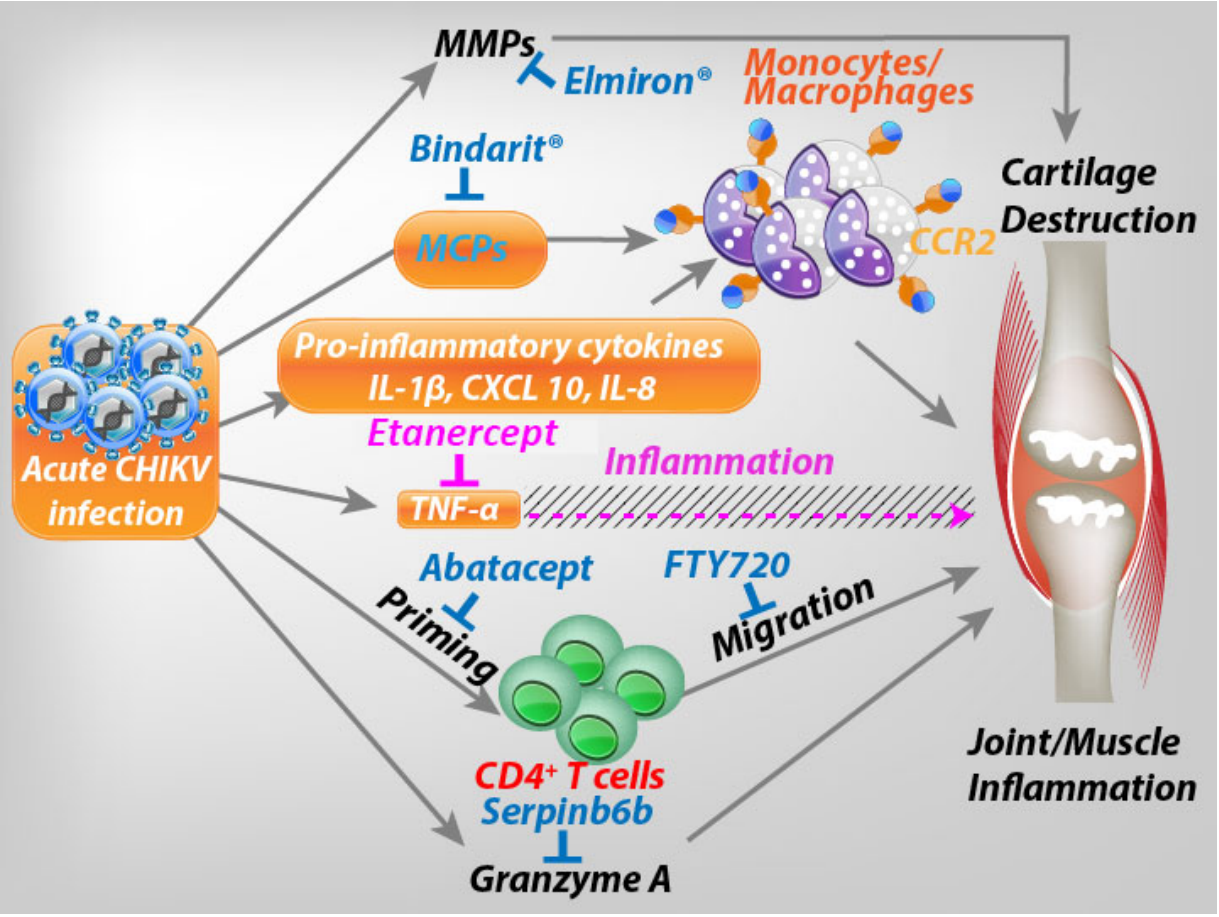

Figure 1. Schematic overview of the mechanisms of tissue inflammation leading to alphaviral arthritis. Based on experimental models of alphavirus infection, key cytokine-dependent inflammatory pathways have been identified and targeted to explore therapeutic avenues. Principally, monocyte chemotactic proteins (MCPs) such as CCL2 and CCL3, which drive monocytic infiltration into joint and muscle tissue in alphaviral inflammation (50,89) (e.g., chikungunya virus [CHIKV] infection), can be targeted using MCP inhibitors such as bindarit, while potent proinflammatory cytokines and chemokines such as interleukin-1 (IL-1), CXCL10, and IL-8 are also the focus of current studies. Scavenging soluble MCPs such as CCL2 restrict CCR2-dependent monocyte/macrophage infiltration, which is required for chikungunya arthritis (87,88). Pentosan polysulfate (Elmiron) has been shown to limit chikungunya virus–induced arthritis and cartilage damage by significantly reducing tissue expression of matrix metalloproteinases (MMPs) that drive cartilage damage in alphaviral infection (92) and in experimental models of cartilage damage (91). RNA sequencing analysis of chikungunya virus–infected tissue in mice has shown a prominent role of granzyme A in driving arthritic inflammation, and the use of the mouse granzyme A inhibitor Serpinb6b was found to dampen tissue inflammation and swelling in chikungunya virus–infected mice (21). In addition to targeting innate inflammatory mechanisms, modulating adaptive immunity has been shown to reduce tissue infiltration, either by inhibiting priming of CD4+ T cells using abatacept (105) or by blocking egress of CD4+ T cells from the lymph nodes to the joints (93) using FTY720 (fingolimod). The role of tumor necrosis factor (TNF) in alphavirus inflammation, despite its prominent expression in the tissues of infected mice and humans, appears to rely on a more complex mechanism. Inhibition of TNF using etanercept in a mouse model of alphaviral arthritis was shown to significantly exacerbate inflammatory disease and cellular infiltration (86), thereby reinforcing the need for a cautious approach when considering biologic therapies for the treatment of alphaviral diseases such as chikungunya virus.

burden at the site of infection, as well as at distant sites, but also diminished the number of activated innate immune cells and levels of proinflammatory cytokines and chemokines (99). Therefore, more studies are needed to examine the utility of neutralizing antibodies as a therapeutic approach to persistent chikungunya virus infection, and to confirm the efficacy of these approaches in humans.

In contrast, studies have shown that prophylactic treatment with chikungunya virus–specific mAb prevents joint inflammation in chikungunya virus–infected wild-type mice and can protect against fatal chikungunya virus infection in AG129, RAG-2$^{-/-}$, and IFNAR-1$^{-/-}$ mice (98–103). Administration of chikungunya virus–specific mAb to RAG-1$^{-/-}$ mice prior to infection resulted in drastically reduced viremia and chikungunya virus RNA levels in ankle joints of animals with persistent chikungunya virus infection (103). Passive immunization with chikungunya virus IgG in IFNα/βR$^{-/-}$ mice also prevented mortality from chikungunya virus infection (102). However, these studies only examined the effect of using mAb as prophylaxis for acute chikungunya virus infection. Thus, our understanding of the prophylactic use of mAb in chronic chikungunya arthritis is still incomplete, and more studies are needed. Nevertheless, prophylactic treatment could be effective for individuals at increased risk of chikungunya virus infection in critical settings, such as mother-to-child transmission (104) or hospitalized individuals with life-threatening acute disease (105).

Combined therapy with biologic agents. A recent study by Miner et al sought to target both humoral and adaptive arms of the immune response by using abatacept, a drug approved in 2005 by the FDA for the treatment of RA, in combination with an anti–chikungunya virus neutralizing antibody, and assessed their ability to decrease acute joint swelling in chikungunya virus–infected mice (106). Abatacept, a human IgG fusion protein paired with a CTLA-4 extracellular domain motif, prevents antigen-presenting cells from delivering costimulatory signals to T cells. In the study by Miner et al, abatacept reduced T cell accumulation in the joints of infected mice and, in combination with an anti–chikungunya virus neutralizing antibody, abolished signs of inflammatory disease and markedly reduced levels of chemokines, proinflammatory cytokines, and infiltrating leukocytes (106). Notwithstanding the promising preclinical outcomes and innovative approaches, these candidate therapies, along with the other examples cited earlier in this review (summarized in Figure 1), warrant further evaluation in the treatment of chikungunya virus–induced joint pathologies in a clinical setting, keeping in mind the potential risk of immunosuppression when targeting host response mechanisms.

Conclusions

Chikungunya virus, a previously neglected tropical arthritogenic alphaviral infection, has gained global significance in the last decade after a series of devastating outbreaks, exposing the severe public health and economic burdens as well as the significant risk of acquired disabilities incurred by international travelers. The clinical and immunopathologic phenotype of this chronic inflammatory rheumatic disease is reminiscent of RA, and studies in animal models of alphaviral infections have helped to elucidate previously unknown mechanisms of disease and brought to light novel therapeutic approaches. Based on its newly recognized public health importance and its strong potential for reemergence, chikungunya arthritis should be the focus of further experimental forays to develop novel therapeutic approaches and should also gain further attention from rheumatologists worldwide.

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AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

REFERENCES

1. Centers for Disease Control and Prevention. Chikungunya virus: 2016 final data for the United States. URL: https://www.cdc.gov/chikungunya/geo/united-states-2016.html.
2. Kuehn BM. Chikungunya virus transmission found in the United States: US health authorities brace for wider spread. JAMA 2014;312:776–7.
3. Seyler T, Hutin Y, Ramanchandran V, Ramakrishnan R, Manickam P, Murhekar M. Estimating the burden of disease and the economic cost attributable to chikungunya, Andhra Pradesh, India, 2005–2006. Trans R Soc Trop Med Hyg 2010;104:133–8.
4. Gould EA, Higgs S. Impact of climate change and other factors on emerging arbovirus diseases. Trans R Soc Trop Med Hyg 2009;103:109–21.
5. Rodríguez-Barraquer I, Solomon SS, Kuganantham P, Srikrishnan AK, Vasudevan CK, Iqbal SH, et al. The hidden burden of dengue and chikungunya in Chennai, India. PLoS Negl Trop Dis 2015;9:e0003906.
6. Soumahoro MK, Gérardin P, Boelle PY, Perrau J, Fianu A, Pouchot J, et al. Impact of chikungunya virus infection on health status and quality of life: a retrospective cohort study. PLoS One 2009;4:e7800.
7. Marimoutou C, Vivier E, Oliver M, Boutin JP, Simon F. Morbidity and impaired quality of life 30 months after chikungunya infection: comparative cohort of infected and uninfected French military policemen in Reunion Island. Medicine (Baltimore) 2012;91:212–9.
8. Marimoutou C, Ferraro J, Javelle E, Deparis X, Simon F. Chikungunya infection: self-reported rheumatic morbidity and

impaired quality of life persist 6 years later. Clin Microbiol Infect 2015;21:688–93.
9. Couturier E, Guillemin F, Mura M, Léon L, Virion JM, Letort MJ, et al. Impaired quality of life after chikungunya virus infection: a 2-year follow-up study. Rheumatology (Oxford) 2012;51: 1315–22.
10. Gérardin P, Fianu A, Malvy D, Mussard C, Boussaïd K, Rollot O, et al. Perceived morbidity and community burden after a chikungunya outbreak: the TELECHIK survey, a population-based cohort study. BMC Med 2011;9:5.
11. Soumahoro MK, Boelle PY, Gaüzere BA, Atsou K, Pelat C, Lambert B, et al. The chikungunya epidemic on La Réunion Island in 2005–2006: a cost-of-illness study. PLoS Negl Trop Dis 2011;5:e1197.
12. Goo L, Dowd KA, Lin TY, Mascola JR, Graham BS, Ledgerwood JE, et al. A virus-like particle vaccine elicits broad neutralizing antibody responses in humans to all chikungunya virus genotypes. J Infect Dis 2016;214:1487–91.
13. Ramsauer K, Schwameis M, Firbas C, Müllner M, Putnak RJ, Thomas SJ, 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 Infect Dis 2015;15:519–27.
14. Abdelnabi R, Neyts J, Delang L. Antiviral strategies against chikungunya virus. Methods Mol Biol 2016;1426:243–53.
15. Abdelnabi R, Neyts J, Delang L. Chikungunya virus infections: time to act, time to treat. Curr Opin Virol 2017;24:25–30.
16. Borgherini G, Poubeau P, Staikowsky F, Lory M, Le Moullec N, Becquart JP, et al. Outbreak of chikungunya on Reunion Island: early clinical and laboratory features in 157 adult patients. Clin Infect Dis 2007;44:1401–7.
17. Staikowsky F, Talarmin F, Grivard P, Souab A, Schuffenecker I, Le Roux K, et al. Prospective study of chikungunya virus acute infection in the Island of La Réunion during the 2005–2006 outbreak. PLoS One 2009;4:e7603.
18. Simon F, Javelle E, Cabie A, Bouquillard E, Troisgros O, Gentile G, et al. French guidelines for the management of chikungunya (acute and persistent presentations): November 2014. Med Mal Infect 2015;45:243–63.
19. Kam YW, Simarmata D, Chow A, Her Z, Teng TS, Ong EK, et al. Early appearance of neutralizing immunoglobulin G3 antibodies is associated with chikungunya virus clearance and long-term clinical protection. J Infect Dis 2012;205:1147–54.
20. Wauquier N, Becquart P, Nkoghe D, Padilla C, Ndjoyi-Mbiguino A, Leroy EM. The acute phase of chikungunya virus infection in humans is associated with strong innate immunity and T CD8 cell activation. J Infect Dis 2011;204:115–23.
21. Wilson JA, Prow NA, Schroder WA, Ellis JJ, Cumming HE, Gearing LJ, et al. RNA-Seq analysis of chikungunya virus infection and identification of granzyme A as a major promoter of arthritic inflammation. PLoS Pathog 2017;13:e1006155.
22. Chow A, Her Z, Ong EK, Chen JM, Dimatatac F, Kwek DJ, et al. Persistent arthralgia induced by chikungunya virus infection is associated with interleukin-6 and granulocyte macrophage colony-stimulating factor. J Infect Dis 2011;203:149–57.
23. Labadie K, Larcher T, Joubert C, Mannioui A, Delache B, Brochard P, et al. Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. J Clin Invest 2010;120:894–906.
24. Couderc T, Chrétien F, Schilte C, Disson O, Brigitte M, Guivel-Benhassine F, et al. A mouse model for chikungunya: young age and inefficient type-I interferon signaling are risk factors for severe disease. PLoS Pathog 2008;4:e29.
25. Gardner CL, Burke CW, Higgs ST, Klimstra WB, Ryman KD. Interferon-α/β deficiency greatly exacerbates arthritogenic disease in mice infected with wild-type chikungunya virus but not with the cell culture-adapted live-attenuated 181/25 vaccine candidate. Virology 2012;425:103–12.
26. Rudd PA, Wilson J, Gardner J, Larcher T, Babarit C, Le TT, et al. Interferon response factors 3 and 7 protect against chikungunya virus hemorrhagic fever and shock. J Virol 2012;86:9888–98.
27. Poddar S, Hyde JL, Gorman MJ, Farzan M, Diamond MS. The interferon-stimulated gene IFITM3 restricts infection and pathogenesis of arthritogenic and encephalitic alphaviruses. J Virol 2016;90:8780–94.
28. Fros JJ, Pijlman GP. Alphavirus infection: host cell shut-off and inhibition of antiviral responses. Viruses 2016;8:E166.
29. Breakwell L, Dosenovic P, Karlsson Hedestam GB, D'Amato M, Liljeström P, Fazakerley J, et al. Semliki Forest virus nonstructural protein 2 is involved in suppression of the type I interferon response. J Virol 2007;81:8677–84.
30. Kelvin AA, Banner D, Silvi G, Moro ML, Spataro N, Gaibani P, et al. Inflammatory cytokine expression is associated with chikungunya virus resolution and symptom severity. PLoS Negl Trop Dis 2011;5:e1279.
31. Chaaitanya IK, Muruganandam N, Sundaram SG, Kawalekar O, Sugunan AP, Manimunda SP, et al. Role of pro-inflammatory cytokines and chemokines in chronic arthropathy in CHIKV infection. Viral Immunol 2011;24:265–71.
32. Teng TS, Kam YW, Lee B, Hapuarachchi HC, Wimal A, Ng LC, et al. A systematic meta-analysis of immune signatures in patients with acute chikungunya virus infection. J Infect Dis 2015; 211:1925–35.
33. Her Z, Malleret B, Chan M, Ong EK, Wong SC, Kwek DJ, et al. Active infection of human blood monocytes by chikungunya virus triggers an innate immune response. J Immunol 2010;184:5903–13.
34. Thanapati S, Das R, Tripathy AS. Phenotypic and functional analyses of NK and NKT-like populations during the early stages of chikungunya infection. Front Microbiol 2015; 6:895.
35. Van Aalst M, Nelen CM, Goorhuis A, Stijnis C, Grobusch MP. Long-term sequelae of chikungunya virus disease: a systematic review. Travel Med Infect Dis 2017;15:8–22.
36. Hoarau JJ, Jaffar-Bandjee MC, Krejbich Trotot P, Das T, Li-Pat-Yuen G, Dassa B, et al. Persistent chronic inflammation and infection by chikungunya arthritogenic alphavirus in spite of a robust host immune response. J Immunol 2010;184: 5914–27.
37. Kwan Tat S, Padrines M, Théoleyre S, Heymann D, Fortun Y. IL-6, RANKL, TNF-α/IL-1: interrelations in bone resorption pathophysiology. Cytokine Growth Factor Rev 2004;15:49–60.
38. Noret M, Herrero L, Rulli N, Rolph M, Smith PN, Li RW, et al. Interleukin 6, RANKL, and osteoprotegerin expression by chikungunya virus-infected human osteoblasts. J Infect Dis 2012;206: 455–7.
39. Chen W, Foo SS, Rulli NE, Taylor A, Sheng KC, Herrero LJ, et al. Arthritogenic alphaviral infection perturbs osteoblast function and triggers pathologic bone loss. Proc Natl Acad Sci U S A 2014;111:6040–5.
40. Fonseca JE, Santos MJ, Canhão H, Choy E. Interleukin-6 as a key player in systemic inflammation and joint destruction. Autoimmun Rev 2009;8:538–42.
41. Rodríguez-Morales AJ, Hoyos-Guapacha KL, Vargas-Zapata SL, Meneses-Quintero OM, Gutiérrez-Segura JC. Would be IL-6 a missing link between chronic inflammatory rheumatism and depression after chikungunya infection? Rheumatol Int 2017; 37:1149–51.
42. Sepúlveda-Delgado J, Vera-Lastra OL, Trujillo-Murillo K, Canseco-Ávila LM, Sánchez-González RA, Gómez-Cruz O, et al. Inflammatory biomarkers, disease activity index, and self-reported disability may be predictors of chronic arthritis after chikungunya infection: brief report. Clin Rheumatol 2017;36: 695–9.
43. Nakaya HI, Gardner J, Poo YS, Major L, Pulendran B, Suhrbier A. Gene profiling of chikungunya virus arthritis in a mouse model

reveals significant overlap with rheumatoid arthritis. Arthritis Rheum 2012;64:3553–63.
44. Gasque P, Jaffar-Bandjee MC. Blunting CHIKV infection by keeping T cells in check. Sci Transl Med 2017;9:eaam6567.
45. Miner JJ, Aw Yeang HX, Fox JM, Taffner S, Malkova ON, Oh ST, et al. Chikungunya viral arthritis in the United States: a mimic of seronegative rheumatoid arthritis. Arthritis Rheumatol 2015;67:1214–20.
46. Thanapati S, Ganu M, Giri P, Kulkarni S, Sharma M, Babar P, et al. Impaired NK cell functionality and increased TNF-α production as biomarkers of chronic chikungunya arthritis and rheumatoid arthritis. Hum Immunol 2017;78:370–4.
47. Lee WW, Teo TH, Her Z, Lum FM, Kam YW, Haase D, et al. Expanding regulatory T cells alleviates chikungunya virus-induced pathology in mice. J Virol 2015;89:7893–904.
48. Lum FM, Teo TH, Lee WW, Kam YW, Renia L, Ng LF. An essential role of antibodies in the control of chikungunya virus infection. J Immunol 2013;190:6295–302.
49. McCarthy MK, Morrison TE. Persistent RNA virus infections: do PAMPS drive chronic disease? Curr Opin Virol 2017;23:8–15.
50. Poo YS, Nakaya H, Gardner J, Larcher T, Schroder WA, Le TT, et al. CCR2 deficiency promotes exacerbated chronic erosive neutrophil-dominated chikungunya virus arthritis. J Virol 2014; 88:6862–72.
51. Santiago L, Menaa C, Arias M, Martin P, Jaime-Sánchez P, Metkar S, et al. Granzyme A contributes to inflammatory arthritis in mice through stimulation of osteoclastogenesis. Arthritis Rheumatol 2017;69:320–34.
52. Rodríguez-Morales AJ, Cardona-Ospina JA, Fernanda Urbano-Garzón S, Sebastian Hurtado-Zapata J. Prevalence of post-chikungunya infection chronic inflammatory arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2016; 68:1849–58.
53. Borgherini G, Poubeau P, Jossaume A, Gouix A, Cotte L, Michault A, et al. Persistent arthralgia associated with chikungunya virus: a study of 88 adult patients on Reunion Island. Clin Infect Dis 2008;47:469–75.
54. Sissoko D, Malvy D, Ezzedine K, Renault P, Moscetti F, Ledrans M, et al. Post-epidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. PLoS Negl Trop Dis 2009;3:e389.
55. Malvy D, Ezzedine K, Mamani-Matsuda M, Autran B, Tolou H, Receveur MC, et al. Destructive arthritis in a patient with chikungunya virus infection with persistent specific IgM antibodies. BMC Infect Dis 2009;9:200.
56. Larrieu S, Pouderoux N, Pistone T, Filleul L, Receveur MC, Sissoko D, et al. Factors associated with persistence of arthralgia among chikungunya virus-infected travellers: report of 42 French cases. J Clin Virol 2010;47:85–8.
57. Manimunda SP, Vijayachari P, Uppoor R, Sugunan AP, Singh SS, Rai SK, et al. Clinical progression of chikungunya fever during acute and chronic arthritic stages and the changes in joint morphology as revealed by imaging. Trans R Soc Trop Med Hyg 2010;104:392–9.
58. Gérardin P, Fianu A, Michault A, Mussard C, Boussaïd K, Rollot O, et al. Predictors of chikungunya rheumatism: a prognostic survey ancillary to the TELECHIK cohort study. Arthritis Res Ther 2013;15:R9.
59. Schilte C, Staikowsky F, Staikovsky F, Couderc T, Madec Y, Carpentier F, et al. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. PLoS Negl Trop Dis 2013;7:e2137.
60. Yaseen HM, Simon F, Deparis X, Marimoutou C. Identification of initial severity determinants to predict arthritis after chikungunya infection in a cohort of French gendarmes. BMC Musculoskelet Disord 2014;15:249.
61. Rahim AA, Thekkekara RJ, Bina T, Paul BJ. Disability with persistent pain following an epidemic of chikungunya in rural South India. J Rheumatol 2016;43:440–4.
62. Javelle E, Ribéra A, Degasne I, Gaüzere BA, Marimoutou C, Simon F. Specific management of post-chikungunya rheumatic disorders: a retrospective study of 159 cases in Reunion Island from 2006–2012. PLoS Negl Trop Dis 2015;9:e0003603.
63. 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 2017. E-pub ahead of print.
64. Suhrbier A, Mahalingam S. The immunobiology of viral arthritides. Pharmacol Ther 2009;124:301–8.
65. Poo YS, Rudd PA, Gardner J, Wilson JA, Larcher T, Colle MA, et al. Multiple immune factors are involved in controlling acute and chronic chikungunya virus infection. PLoS Negl Trop Dis 2014;8:e3354.
66. Messaoudi I, Vomaske J, Totonchy T, Kreklywich CN, Haberthur K, Springgay L, et al. Chikungunya virus infection results in higher and persistent viral replication in aged rhesus macaques due to defects in anti-viral immunity. PLoS Negl Trop Dis 2013;7:e2343.
67. Hoarau JJ, Gay F, Pellé O, Samri A, Jaffar-Bandjee MC, Gasque P, et al. Identical strength of the T cell responses against E2, nsP1 and capsid CHIKV proteins in recovered and chronic patients after the epidemics of 2005–2006 in La Reunion Island. PLoS One 2013;8: e84695.
68. Narendra SC, Chalise JP, Höök N, Magnusson M. Dendritic cells activated by double-stranded RNA induce arthritis via autocrine type I IFN signaling. J Leukoc Biol 2014;95:661–6.
69. Ozden S, Huerre M, Riviere JP, Coffey LL, Afonso PV, Mouly V, et al. Human muscle satellite cells as targets of chikungunya virus infection. PLoS One 2007;2:e527.
70. Motohashi N, Asakura A. Muscle satellite cell heterogeneity and self-renewal. Front Cell Dev Biol 2014;2:1.
71. Mylonas AD, Harley D, Purdie DM, Pandeya N, Vecchio PC, Farmer JF, et al. Corticosteroid therapy in an alphaviral arthritis. J Clin Rheumatol 2004;10:326–30.
72. Suhrbier A, Jaffar-Bandjee MC, Gasque P. Arthritogenic alphaviruses: an overview. Nat Rev Rheumatol 2012;8:420–9.
73. De Lamballerie X, Boisson V, Reynier JC, Enault S, Charrel RN, Flahault A, et al. On chikungunya acute infection and chloroquine treatment. Vector Borne Zoonotic Dis 2008;8:837–9.
74. 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.
75. 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. Indian J Rheumatol 2009;4:94–101.
76. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29–36.
77. Gallegos KM, Drusano GL, D'Argenio DZ, Brown AN. Chikungunya virus: in vitro response to combination therapy with ribavirin and interferon alfa 2a. J Infect Dis 2016;214:1192–7.
78. Delang L, Segura Guerrero N, Tas A, Quérat G, Pastorino B, Froeyen M, et al. Mutations in the chikungunya virus non-structural proteins cause resistance to favipiravir (T-705), a broad-spectrum antiviral. J Antimicrob Chemother 2014;69:2770–84.
79. Albulescu IC, van Hoolwerff M, Wolters LA, Bottaro E, Nastruzzi C, Yang SC, et al. Suramin inhibits chikungunya virus replication through multiple mechanisms. Antiviral Res 2015;121: 39–46.
80. Mounce BC, Cesaro T, Carrau L, Vallet T, Vignuzzi M. Curcumin inhibits Zika and chikungunya virus infection by inhibiting cell binding. Antiviral Res 2017;142:148–57.
81. Karlas A, Berre S, Couderc T, Varjak M, Braun P, Meyer M, et al. A human genome-wide loss-of-function screen identifies effective chikungunya antiviral drugs. Nat Commun 2016;7:11320.

82. Bouquillard E, Combe B. A report of 21 cases of rheumatoid arthritis following chikungunya fever. a mean follow-up of two years. Joint Bone Spine 2009;76:654–7.
83. Mathew AJ, Goyal V, George E, Thekkemuriyil DV, Jayakumar B, Chopra A, et al. Rheumatic-musculoskeletal pain and disorders in a naïve group of individuals 15 months following a chikungunya viral epidemic in south India: a population based observational study. Int J Clin Pract 2011;65:1306–12.
84. 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.
85. Martí-Carvajal A, Ramon-Pardo P, Javelle E, Simon F, Aldighieri S, Horvath H, et al. Interventions for treating patients with chikungunya virus infection-related rheumatic and musculoskeletal disorders: a systematic review. PLoS One 2017;12:e0179028.
86. Ganu MA, Ganu AS. Post-chikungunya chronic arthritis: our experience with DMARDs over two year follow up. J Assoc Physicians India 2011;59:83–6.
87. Zaid A, Rulli NE, Rolph MS, Suhrbier A, Mahalingam S. Disease exacerbation by etanercept in a mouse model of alphaviral arthritis and myositis. Arthritis Rheum 2011;63:488–91.
88. Chen W, Foo SS, Taylor A, Lulla A, Merits A, Hueston L, et al. Bindarit, an inhibitor of monocyte chemotactic protein synthesis, protects against bone loss induced by chikungunya virus infection. J Virol 2015;89:581–93.
89. Rulli NE, Rolph MS, Srikiatkhachorn A, Anantapreecha S, Guglielmotti A, Mahalingam S. Protection from arthritis and myositis in a mouse model of acute chikungunya virus disease by bindarit, an inhibitor of monocyte chemotactic protein-1 synthesis. J Infect Dis 2011;204:1026–30.
90. Vergunst CE, Gerlag DM, Lopatinskaya L, Klareskog L, Smith MD, van den Bosch F, et al. Modulation of CCR2 in rheumatoid arthritis: a double-blind, randomized, placebo-controlled clinical trial. Arthritis Rheum 2008;58:1931–9.
91. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol 1987;138:513–6.
92. Kumagai K, Shirabe S, Miyata N, Murata M, Yamauchi A, Kataoka Y, et al. Sodium pentosan polysulfate resulted in cartilage improvement in knee osteoarthritis: an open clinical trial. BMC Clin Pharmacol 2010;10:7.
93. Herrero LJ, Foo SS, Sheng KC, Chen W, Forwood MR, Bucala R, et al. Pentosan polysulfate: a novel glycosaminoglycan-like molecule for effective treatment of alphavirus-induced cartilage destruction and inflammatory disease. J Virol 2015;89:8063–76.
94. Teo TH, Chan YH, Lee WW, Lum FM, Amrun SN, Her Z, et al. Fingolimod treatment abrogates chikungunya virus-induced arthralgia. Sci Transl Med 2017;9:eaal1333.
95. Long F, Fong RH, Austin SK, Chen Z, Klose T, Fokine A, et al. Cryo-EM structures elucidate neutralizing mechanisms of anti-chikungunya human monoclonal antibodies with therapeutic activity. Proc Natl Acad Sci U S A 2015;112: 13898–903.
96. Fox JM, Long F, Edeling MA, Lin H, van Duijl-Richter MK, Fong RH, et al. Broadly neutralizing alphavirus antibodies bind an epitope on E2 and inhibit entry and egress. Cell 2015;163: 1095–107.
97. Smith SA, Silva LA, Fox JM, Flyak AI, Kose N, Sapparapu G, et al. Isolation and characterization of broad and ultrapotent human monoclonal antibodies with therapeutic activity against chikungunya virus. Cell Host Microbe 2015;18: 86–95.
98. Hawman DW, Fox JM, Ashbrook AW, May NA, Schroeder KM, Torres RM, et al. Pathogenic chikungunya virus evades B cell responses to establish persistence. Cell Rep 2016;16:1326–38.
99. Broeckel R, Fox JM, Haese N, Kreklywich CN, Sukulpovi-Petty S, Legasse A, et al. Therapeutic administration of a recombinant human monoclonal antibody reduces the severity of chikungunya virus disease in rhesus macaques. PLoS Negl Trop Dis 2017;11: e0005637.
100. Pal P, Dowd KA, Brien JD, Edeling MA, Gorlatov S, Johnson S, et al. Development of a highly protective combination monoclonal antibody therapy against chikungunya virus. PLoS Pathog 2013;9:e1003312.
101. Fric J, Bertin-Maghit S, Wang CI, Nardin A, Warter L. Use of human monoclonal antibodies to treat chikungunya virus infection. J Infect Dis 2013;207:319–22.
102. Couderc T, Khandoudi N, Grandadam M, Visse C, Gangneux N, Bagot S, et al. Prophylaxis and therapy for chikungunya virus infection. J Infect Dis 2009;200:516–23.
103. Hawman DW, Stoermer KA, Montgomery SA, Pal P, Oko L, Diamond MS, et al. Chronic joint disease caused by persistent chikungunya virus infection is controlled by the adaptive immune response. J Virol 2013;87:13878–88.
104. Gérardin P, Barau G, Michault A, Bintner M, Randrianaivo H, Choker G, et al. Multidisciplinary prospective study of mother-to-child chikungunya virus infections on the island of La Réunion. PLoS Med 2008;5:e60.
105. Lémant J, Boisson V, Winer A, Thibault L, André H, Tixier F, et al. Serious acute chikungunya virus infection requiring intensive care during the Reunion Island outbreak in 2005–2006. Crit Care Med 2008;36:2536–41.
106. Miner JJ, Cook LE, Hong JP, Smith AM, Richner JM, Shimak RM, et al. Therapy with CTLA4-Ig and an antiviral monoclonal antibody controls chikungunya virus arthritis. Sci Transl Med 2017;9:eaah3438.