limitations of our evaluation of the cohort was that we have not yet determined the incidence of rheumatoid factor (RF) and anti–cyclic citrullinated peptide (anti-CCP) antibodies in all 485 patients. This will be a valuable assessment to perform. However, RF and anti-CCP antibodies were measured in a subset of chikungunya arthritis patients (Chang AY, Martins K, Encinales L, Reid SP, Acuña M, Encinales C, et al. Chikungunya arthritis mechanisms in the Americas: a cross-sectional analysis of chikungunya arthritis patients twenty-two months after infection demonstrating no detectable viral persistence in synovial fluid. Arthritis Rheumatol 2018;70:585–93) and none of these patients had elevated levels of anti-CCP antibodies, 9% had IgM-RF, and 12% had IgG-RF. In addition, we agree that rigorous controlled trials of therapeutics including methotrexate for the treatment of chikungunya arthritis are needed to set evidence-based guidelines for treatment. Open-label studies in arthritis and pain can be confounded by many issues that make it difficult to interpret the data, including placebo effects.

To clarify the timing of blood collection in our study, 343 of the 485 patients with confirmed chikungunya (71%) had their blood drawn within the first month of their febrile illness. It is unlikely that the patients in this cohort with IgG were previously infected with chikungunya, as all of the samples were collected in January 2015 during a chikungunya epidemic in a region where the virus had not previously circulated.

We also agree that further standardized tools for assessment of the chronic manifestations of chikungunya are needed, including patient-reported health outcomes. The Disease Activity Score in 28 joints was developed primarily for rheumatoid arthritis but is being used in many other types of arthritis. Even so, a validated customized measure for chikungunya arthritis would be important for clinical trials and regulatory approvals. The Patient-Reported Outcomes Measurement Information System (PROMIS), which collects information on patient stiffness, mobility, pain, and mental health, is one possibility. PROMIS is a system developed by multiple academic medical centers, private research organizations, and numerous institutes across the National Institutes of Health (Witter JP. The promise of patient-reported outcomes measurement information system—turning theory into reality: a uniform approach to patient-reported outcomes across rheumatic diseases. Rheum Dis Clin North Am 2016;42:377–94). The use of a standardized and validated measure such as PROMIS should be encouraged so that we can compare across our studies. However, the use of patient-derived outcomes will probably require additional traditional measures of disease severity for regulatory approval.

Aileen Y. Chang, MD, MSPH
Jeffrey M. Bethony, PhD
Gary L. Simon, MD, PhD
George Washington University
Washington, DC
Liliana Encinales, MD
Allied Research Society
Barranquilla, Colombia
Gary S. Firestein, MD
University of California, San Diego

DOI 10.1002/art.40665

Autoimmunity or lineage-specific virulence as drivers of chikungunya chronic arthritis: comment on the article by Chang et al

To the Editor:

We read with interest the article by Chang et al reporting the absence of detectable virus in the synovial fluid of chikungunya arthritis patients (1). Although tissue biopsies were not performed, the authors provide compelling arguments against the hypothesis of viral persistence in the pathophysiology of chikungunya arthritis (2), based on the negative findings of both synovial fluid culture and proteomic analysis. Furthermore, given the presumption of efficacy of disease-modifying antirheumatic drugs, the authors conclude, as others have before them (2), that autoimmunity may be the leading contributor to chikungunya arthritis. In addition, they propose that chikungunya virus debris may persist at low levels as triggering antigens for autoimmunity, or that macrophages may be modified through epigenetic imprinting, similar to fibroblast-like synoviocytes in rheumatoid arthritis (RA), resulting in persistent alterations in host gene transcriptions.

We wish to corroborate their findings and propose two other hypotheses to support the clinical pattern of the moderately active seronegative polyarthritis that they primarily observed. For this purpose, we used a benchmarking of cohort studies conducted on Réunion Island populations infected with the East Central South African–diverged clade (also known as Indian Ocean lineage [IOL]) of chikungunya and compared the results to those acquired in Colombia with the Asian strain of chikungunya. We graded the severity of chikungunya arthritis according to Disease Activity Score in 28 joints (3), when available, or by the prevalence of synovitis (1 [mild] to 4 [severe], with 4 fulfilling the American College of Rheumatology/European League Against Rheumatism criteria for RA) (4).

As seen in Supplementary Table 1 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40665/abstract), our investigation showed that the severity of reported chikungunya arthritis likely increases from the community to the primary care setting (as a result of more synovitis case recruitment), and from the primary care to the rheumatologist (as a result of more polyarticular injury with severe erosive arthritis). Except in rare cases of seropositive RA, the severity of chikungunya arthritis does not seem to correlate with the presence of rheumatoid factor. Moreover, anti-citrullinated cyclic peptide (anti-CCP) antibodies are infrequent, even in the setting of prominent symmetric polyarticular injury, which suggests an operating mechanism other than autoimmunity. Indeed, citrulline biosynthesis could be inhibited during the acute stage of chikungunya through massive repression of the synthesis of its 2 precursors in the urea cycle, carbamyl phosphate (5–37-fold change) and L-ornithine (20-fold change) (4). Along with the absence of other anti-CCP antibodies known to be associated with severe erosive forms of RA, this would account for the moderate activity of chikungunya polyarthritis observed in Colombia (1). In addition, given the correlation between high viral loads and chronicity (2), less acute joint pathology with the Asian strain

of chikungunya (compared to IOL)—due to a lower capacity for inducing proinflammatory Th1 and natural killer cell responses (5)—could be another possible explanation for this observation.

Patrick Gérardin, MD, PhD
Centre Hospitalier Universitaire, INSERM CIC1410 Saint Pierre, Réunion, France and UMR 134 PIMIT (CNRS 9192 INSERM 1187 IRD 249 Universite de la Réunion) Sainte Clotilde, Réunion, France
Jaime A. Cardona-Ospina, MD
Alfonso J. Rodríguez-Morales, MD, MSc, HonDSc
Universidad Tecnologica de Pereira Pereira, Colombia

1. Chang AY, Martins KA, Encinales L, Reid SP, Acuna M, Encinales C, et al. Chikungunya arthritis mechanisms in the Americas: a cross-sectional analysis of chikungunya arthritis patients twenty-two months after infection demonstrating no detectable viral persistence in synovial fluid. Arthritis Rheumatol 2018;70:585–93.
2. Zaid A, Gérardin P, Taylor A, Mostafavi H, Malvy D, Mahalingam S. Chikungunya arthritis: implications of acute and chronic inflammation mechanisms on disease management [review]. Arthritis Rheumatol 2018;70:488–95.
3. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
4. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.
5. Dhanwani R, Khan M, Alam SI, Rao PV, Parida M. Differential proteome analysis of chikungunya virus-infected new-born mice tissues reveals implication of stress, inflammatory and apoptotic pathways in disease pathogenesis. Proteomics 2011;11:1936–51.
6. Teo TH, Her Z, Tan JJ, Lum FM, Lee WW, Chan YH, et al. Caribbean and La Réunion chikungunya virus isolates differ in their capacity to induce pro-inflammatory Th1 and NK cell responses and acute joint pathology. J Virol 2015;89:7955–69.

DOI 10.1002/art.40664

Reply

To the Editor:

We thank Dr. Gérardin et al for sharing their thoughts on potential mechanisms that might contribute to the pathogenesis of chikungunya arthritis. Although we did not observe anti-CCP antibodies in our cohort, posttranslational modifications including citrullination, carbamylation, and malondialdehyde–acetaldehyde are emerging as having clinical and mechanistic significance in rheumatoid arthritis. Therefore, one can postulate that these modifications may have clinical and mechanistic significance in the context of viral-induced arthritis as well, and that further research into these mechanisms in chikungunya arthritis is needed.

With regard to the possibility of proinflammatory T cell responses, we are actively investigating the contribution of adaptive immunity. Studies on peripheral blood and synovial tissue T cell antigen specificity will be important, and we are currently studying whether chronic chikungunya arthritis occurs in the context of aberrant epigenetic marks. Understanding the pathogenesis and developing targeted therapy is urgently needed, as chikungunya outbreaks occur with increasing frequency and can limit mobility for affected individuals.

Aileen Y. Chang, MD, MSPH
Jeffrey M. Bethony, PhD
Gary L. Simon, MD, PhD
George Washington University Washington, DC
St. Patrick Reid, PhD
University of Nebraska Omaha, NE
Liliana Encinales, MD
Allied Research Society Barranquilla, Colombia
Gary S. Firestein, MD
University of California, San Diego

DOI 10.1002/art.40586

T follicular regulatory cells are decreased in patients with established treated rheumatoid arthritis with active disease: comment on the article by Liu et al

To the Editor:

We read with great interest the article by Liu et al (1), in which the authors reported that T follicular regulatory (Tfr) cell levels are increased in untreated rheumatoid arthritis (RA) patients, especially in those whose disease is in stable remission, where the Tfr to T follicular helper (Tfh) ratio is also increased. However, in our own cohort of RA patients, we observed results that conflict with the conclusions drawn by the authors.

In a recent study, we defined the phenotype and function of human circulating Tfr cells (2). We used the same gating strategy as described by Liu and colleagues (Figure 1A), in 43 patients with established RA (86% female, mean ± SD age 56 ± 13 years, mean ± SD disease duration 11 ± 9 years), who were treated with methotrexate, with or without other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or glucocorticoids. We found a decrease in Tfr cells and in the Tfr:Tfh ratio in patients with active RA (defined by a Disease Activity Score in 28 joints [DAS28] of >3.2 [3]), compared to age- and sex-matched healthy controls (Figures 1B and C). Unlike Liu et al, we observed no differences between patients with inactive RA and healthy controls. We found the same pattern for Treg cells, which were decreased in patients with active RA, similar to the findings of Liu et al, but not in patients with RA in remission or with low disease activity (Figure 1D). We were also unable to confirm Liu and colleagues' findings that circulating Tfh and programmed death 1 (PD-1)–positive Tfh cells are increased in RA patients, regardless of disease activity (Figures 1E and F). In fact, we found that in patients with inactive RA, the frequency of PD-1+ Tfh cells was less than that found in healthy