Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

targeted, more mechanism-focused therapies are likely to be more successful for treating inclusion body myositis compared with general immunosuppressants. The RAPAMI team observed dysregulation of effector CD8 T cells and regulatory T cells in inclusion body myositis,[2,3] making sirolimus a logical drug choice by virtue of its ability to regulate these specific immune cells.[4] This lesson in drug selection might also hold true for other complex neurodegenerative diseases. For example, in amyotrophic lateral sclerosis, a lethal neurodegenerative disease characterised by changes in specific immune cell populations,[7] general immunosuppression has not improved clinical outcomes, suggesting more focused immune-based clinical trials are needed. Second, the RAPAMI trial emphasised the importance of factoring in disease severity when selecting an optimal clinical trial endpoint in a slowly progressive chronic disease. In RAPAMI, patients with inclusion body myositis were severely impaired, which led the investigators to use the rate of change in quadriceps strength as the primary outcome. However, the trial results suggest that a functional test, such as 6-min walking distance, might be a more relevant marker of both disease progression and drug efficacy in a disabled patient population. Finally, RAPAMI emphasised how crucial it is to determine the time course and type of immune dysregulation in inclusion body myositis, and whether it is causative or secondary to other dysregulated pathways. These findings would guide the optimal timing during the disease course for administering sirolimus, or other targeted immunotherapies, to produce maximum benefit.

Failures and successes from RAPAMI[4] and other clinical trials[1] have cumulatively lent insight and identified the steps necessary to advance targeted, mechanism-based drug discovery for inclusion body myositis. Collectively, we agree with the authors that the beneficial effects of sirolimus in RAPAMI advocate its use in a phase 3 trial, particularly considering its established safety profile[8] and low cost, and the lack of available treatments for inclusion body myositis. Six (27%) patients with inclusion body myositis in the placebo group versus ten (45%) patients in the sirolimus group presented with serious side-effects in the RAPAMI trial, mostly related to sirolimus.[4] Four patients on sirolimus had to permanently discontinue use. However, canker sores, the most common sirolimus side-effect, were mild or moderate. Nonetheless, because of the slowly progressive nature of inclusion body myositis, the long-term effects of sirolimus administration will need to be evaluated. Although the cost of sirolimus is relatively low, cost remains a consideration in inclusion body myositis or any chronic disease, as we have advocated in polyneuropathy,[9] another gradually advancing condition.

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First flare of ACPA-positive rheumatoid arthritis after SARS-CoV-2 infection

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Rheumatoid arthritis is multifactorial and is the most common chronic inflammatory rheumatic disease. In many patients, two elements are central in the development of rheumatoid arthritis: autoantibodies directed against citrulline residues (anti-citrullinated peptide antibodies [ACPAs]),[1] which can be detected in serum up to 15 years

before the onset of clinical symptoms; and the presence of human leukocyte antigen (HLA)-DR alleles that express the so-called shared epitope that is associated with a high risk of developing rheumatoid arthritis.[2] Why clinical polyarthritis occurs in some individuals with these elements is unknown, but external factors such as viral infection could act as a trigger. Indeed, although a definitive mechanistic link between viruses and the induction of autoreactivity is far from established, several studies in humans and animals have shown that viruses can induce or protect the host from autoimmune disease, depending on several factors including genetic background of the host, immune responses to infection, virus strain, viral load, and the timing of infection.[3]

The COVID-19 pandemic that began in 2019 is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which induces various influenza-like symptoms, as well as anosmia, diarrhoea, osteoarticular disorders, and, in severe cases, a possible cytokine storm.[4] Here, we describe a case of ACPA-positive rheumatoid arthritis that occurred immediately after SARS-CoV-2 infection and discuss the potential for SARS-CoV-2 to act as an activator of clinical rheumatoid arthritis.

A 60-year-old woman from Marseille, France, with a healthy body-mass index (20 kg/m^2) and no notable medical history (including no articular signs or symptoms) began to have cough with unusual asthenia, myalgia, abdominal pain, and headaches on April 27, 2020, when the COVID-19 case rate was very high in France. On May 1, 2020, she consulted the University Hospital for Infectious Diseases in Marseille. An RT-PCR for SARS-CoV-2 was positive, and a chest CT scan showed the presence of a nodular condensation with a frosted glass aspect, and essentially subpleural involvement, supporting a diagnosis of a mild SARS-CoV-2 infection. The patient was treated with hydroxychloroquine and azithromycin for 5 days and effizinc (zinc gluconate) for 10 days. Her symptoms improved in within 5–6 days, and a repeat SARS-CoV-2 PCR test (done 11 days after the first symptoms) was negative.

On May 21, 2020, 25 days after the first signs of infection, the patient began to have pain in her right hand, particularly the metacarpophalangeal and interphalangeal joints of the fifth finger, with swelling. 3–5 days later, arthritis had spread to the metacarpophalangeal joints of the first finger on her left hand and the second and third fingers on her right hand; she also had persistent morning stiffness in her hands. Because of lasting pain, she consulted the rheumatology department at Sainte Marguerite Hospital, Marseille, in June, 2020. A set of tests was run on samples taken before and after the onset of arthritis symptoms (appendix pp 1–4).

See Online for appendix

Her serum concentration of anti-cyclic citrullinated (CCP) 2 antibodies were just above the detection limit (20 relative units [RU]/mL) on May 1, 2020, but had increased to 76 RU/mL on July 15, 2020. An anti-CCP3 antibody test was positive, at 450 RU/mL (detection limit 20 RU/mL) on May 1, and had increased to 625 RU/mL on July 15, 2020. Her serum was negative for rheumatoid factor on May 1, and remained around the detection limit (20 RU/mL) on June 8 (23 RU/mL) and on July 15 (21 RU/mL). Her serum concentration of interleukin (IL)-6 gradually increased from the detection limit (2 pg/mL) on May 1 to 31 pg/mL on July 15, 2020.

The patient's serum titre of anti-nuclear antibodies was 1/1280, with a speckled pattern, on both June 8 and July 15; her anti-DNA antibody concentration was 17 IU/mL (detection limit 15 IU/mL) on July 15. Testing for anti-Sjögren's-syndrome-related antigen (SS) A and B antibodies was positive on July 15 (anti-SSA >240 arbitaray units [AU]/mL; anti-SSB >79 AU/mL). The patient tested positive for anti-peptidyl arginine deiminase (anti-PAD) 4 and anti-PAD2 IgG antibodies from May 1, and these antibodies remained detectable at later timepoints. No IgM anti-PAD2 or anti-PAD4 antibodies were detected at any timepoints.

On July 15, 2020, the patient's sedimentation rate was at 97 mm, her serum C-reactive protein concentration increased from normal (<10 mg/L) on May 1 to 18·5 mg/L on July 15. Electrophoresis showed an increase in polyclonal serum immunoglobulins. HLA genotyping showed that the patient did not have the classic shared epitope (genotype: *HLA-A*01:01*, *HLA-A*02:01*; *HLA-B*08:01*, *HLA-B*1402*; *HLA-C*07:01*, *HLA-C*08:02*; *HLA-DRB1*15:01*, *HLA-DRB1*--*; *HLA-DQB1*06:02*, *HLA-DQB1*--*).

Proliferation assays to detect T-cell responses to PAD4 (and peptide 8 from PAD4) were positive on July 15, 2020, but no proliferative response to PAD2 was detected. A T-cell proliferative response was also observed for citrullinated fibrinogen, but not for native fibrinogen. Flow cytometry analysis of intracellular tumour necrosis factor expression after in-vitro stimulation with PAD4, peptide 8 from PAD4, and PAD2 confirmed the presence

of antigen-specific CD4+ T cells specific for PAD4 and proliferative responses to PAD4 and peptide 8 from PAD4, and slight proliferation to PAD2.

X-ray scans of the patient's hands, wrists, and feet on July 15 showed no signs of erosion. Ultrasonography showed numerous zones of cold synovitis and Doppler signals on the patient's hands, but no erosion was found. The patient was diagnosed with ACPA-positive rheumatoid arthritis that fulfilled the 2010 American College of Rheumatology and European League Against Rheumatism criteria. She commenced treatment with methotrexate (10 mg/week) on July 20, 2020, to which she had a good clinical response. We postulate that SARS-CoV-2 infection might have had a role in the clinical onset of rheumatoid arthritis in this patient.

A case of a transient oligoarthritis of the feet that developed after a SARS-CoV-2 infection has been previously reported.[5] This case occurred in a patient with HLA-B27, with no evidence for hyperuricaemia, and neither rheumatoid factor nor ACPAs were present in their serum.[5] A case of ACPA-positive rheumatoid arthritis has previously been described after SARS-CoV-2 infection, but those authors did not measure autoantibody levels before the onset of symptomatic arthritis.[6]

Here, we carefully monitored the patient's autoantibodies from the beginning of their SARS-CoV-2 infection to the onset of clinical rheumatoid arthritis. Notably, ACPAs were already detectable when the patient tested positive for SARS-CoV-2; however, by the time she developed arthritis, her ACPA titres had substantially increased. Infectious agents are known to trigger rheumatoid arthritis flares; indeed, any system-wide inflammatory response might increase inflammatory markers (eg, IL-6, sedimentation rate). However, increasing ACPA titres could indicate epitope spreading before clinical onset of arthritic disease,[7] suggesting that SARS-CoV-2 infection might have precipitated an initial flare of rheumatoid arthritis in this patient.

Two studies of individuals positive for SARS-CoV-2 identified an association between *HLA-DRB1*15:01* and *HLA-DQB1*06:02* and an increased likelihood of testing positive for the virus,[8] suggesting the possibility of impaired presentation of viral peptides necessary to elicit a protective T-cell response.[9] As such, the presence of homozygous *HLA-DRB1*15:01* and *HLA-DQB1* alleles in our patient could have had an effect on the quality of cellular immune responses generated in response to SARS-CoV-2 infection. Our patient had antibody responses and T-cell proliferation to PAD4 and peptide 8 from PAD4, consistent with the hapten-carrier model in rheumatoid arthritis.[10]

To the best of our knowledge, this is the first definitive case of ACPA-positive rheumatoid arthritis developing after SARS-CoV-2 infection (ie, with samples taken before and after arthritis onset), with infection as a potential trigger for epitope spreading and onset of clinical rheumatoid arthritis symptoms.

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