receiving biologic DMARDs is well known, and patients have probably been informed of this risk at the time of treatment initiation (6,7).

Reduced physical activity resulting from home confinement could be another explanation for worsening symptoms. In SpA patients, exercise can reduce disease activity and, consequently, is recommended for optimal treatment (8).

In this patient population, COVID-19 occurrence was associated with SpA treatment modification. We did not find a link between NSAID or biologic treatment and COVID-19. When considering both the confirmed and the clinically suspected cases of COVID-19, we found 31 cases (13 clinically suspicious and 18 self-reported as being confirmed), which is more substantial than the 8 cases in a cohort of 320 patients with chronic arthritis (4 confirmed and 4 highly suggestive) reported by Monti et al (9). However, it is impossible to compare prevalence as the population, methodology, and period are different (9). It is important to emphasize that a majority of our patients were treated with NSAIDs. Our results are interesting because they provide data from a real-life setting.

Our findings should be interpreted within the limitations of the study. The most important limitation is that our results are based on self-reported data. For patients who reported having confirmed COVID-19, we could not verify that this was in fact confirmed via a positive test result. However, this is the first study providing information on therapy compliance during home confinement and reporting the frequency of COVID-19 in SpA patients. The size of our cohort reinforces the importance of our results.

Thus, our survey results show that in SPA patients, home confinement linked to the COVID-19 pandemic is associated with worsening of the disease and reduction or suspension of medication intake, in particular NSAIDs. These findings have considerable clinical implications, given that home confinement is likely to recur in the future. Patients need to be educated about the current evidence regarding NSAID treatment and ways to stay physically active at home.

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1. Sveaas SH, Berg IJ, Provan SA, Semb AG, Hagen KB, Vøllestad N, et al. Efficacy of high intensity exercise on disease activity and cardiovascular risk in active axial spondyloarthritis: a randomized controlled pilot study. PLoS One 2014;9:e108688.
2. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? Ecancermedicalscience 2020;14:1023.
3. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, et al. American College of Rheumatology guidance for the management of adult patients with rheumatic disease during the COVID-19 pandemic: version 1. Arthritis Rheumatol 2020;72:1241–51.
4. Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2019;71:1599–13.
5. Macfarlane GJ, Pathan E, Jones GT, Dean LE. Predicting response to anti-TNFα therapy among patients with axial spondyloarthritis (axSpA): results from BSRBR-AS. Rheumatology (Oxford) 2020. E-pub ahead of print.
6. Menegatti S, Bianchi E, Rogge L. Anti-TNF therapy in spondyloarthritis and related diseases: impact on the immune system and prediction of treatment responses [review]. Front Immunol 2019;10:382.
7. Minozzi S, Bonovas S, Lytras T, Pecoraro V, González-Lorenzo M, Bastiampillai AJ, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf 2016;15 Suppl 1:11–34.
8. Van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978–91.
9. Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies [letter]. Ann Rheum Dis 2020;79:667–8.

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Morbidity and mortality from COVID-19 are not increased among children or patients with autoimmune rheumatic disease—possible immunologic rationale: comment on the article by Henderson et al

To the Editor:

We read with great interest the article by Henderson et al (1) on the therapeutic rationale for using glucocorticoids to treat the hyperinflammation and cytokine storm phases of severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) infection. We would like to expand on their analysis and discuss the data reported to date on the likelihoood of serious outcomes of infection in children and patients with autoimmune rheumatic diseases (rheumatoid arthritis [RA] and systemic lupus erythematosus [SLE]).

To date, children and patients with autoimmune disease have rarely experienced progression of their infection to cytokine release syndrome, the third phase of coronavirus disease 2019 (COVID-19), with few being admitted to intensive care units

(ICUs). Based on reports to date from China, Europe, and the US, patients with rheumatic diseases are not necessarily at increased risk for severe outcomes. The latest report from the COVID-19 Global Rheumatology Alliance (2) shows that of 334 registered patients infected with COVID-19 (of whom 74.25% were women and 25.75% were men), only 38 were hospitalized and 19 (5.69%) died. Within this population of patients with COVID-19, there were 121 patients with RA, 33 with psoriatic arthritis, 58 with SLE, 28 with axial spondyloarthritis, 27 with vasculitis, and 19 with primary Sjögren's syndrome. In China, of 171 children with COVID-19 infection, only 12 experienced radiologic pneumonitis and only 1 died in the pediatric ICU (3). This percentage does not appear to be higher than the percentage in the general population, despite the fact that >65% of adult patients with rheumatic diseases were treated with disease-modifying antirheumatic drugs (DMARDs): 5.39% with JAK inhibitors, 36.5% with biologic DMARDs, and 30.2% with glucocorticoids. Only 25.7% were treated with hydroxychloroquine (HCQ) (2). The Global Rheumatology Alliance data on patients with rheumatic diseases showed that the number of women infected with COVID-19 was higher than the number of men. This is expected, based on data from the general population showing that women with rheumatic diseases are more often hospitalized and more often have a worse disease course. Meanwhile, no proven cases of macrophage activation syndrome or hemophagocytic lymphohistocytosis in children with COVID-19 infection have been described to date. The recently described Kawasaki-like illness (4) still needs to be well defined.

In addition to the potential role of sex, we would like to speculate on the immunologic basis for rheumatic disease patients not having more severe outcomes, as might have been expected at the onset of this pandemic. In the early phases of infection, the lungs of patients with COVID-19 exhibit edema, a patchy inflammatory infiltrate, and multinucleated giant cells (MGCs), with lymphopenia in the peripheral blood. Evidence from animal models demonstrates that macrophage colony-stimulating factor and granulocyte–macrophage colony-stimulating factor stimulate the differentiation of rat alveolar macrophages into MGCs with distinct phenotypes (type 1 and type 2 MGC) and that neutralization of endogenous interleukin-6 (IL-6) during alveolar macrophage differentiation into MGCs significantly inhibits the formation of type 2 MGCs (up to 50%) (5). Of interest, another type of key immune cell, type 2 innate lymphoid cells (ILC2), which are important for maintaining lung integrity, do not efficiently migrate from the bone marrow to the lungs with aging. In mice, transfer of young ILC2 to the old lung enhances resistance to infection. In addition, levels of tumor necrosis factor and IL-6 and numbers of neutrophils increase with age and may contribute to increased inflammation in the lungs. Furthermore, it is well known that IL-6 inhibits natural killer (NK) cell cytotoxicity. Therefore, IL-6 appears to be a key molecule.

Numbers of NK cells are higher in infancy and decrease progressively with aging. Lymphocyte number and function also decline with age, and CD8+ T cells decline in number and weaken with aging, a feature of immunoesenescence (6). We do not yet know if vaccinations administered in early childhood play a role in stimulating the immune system. This is an area of intense clinical research. It has been suggested that SARS–CoV-2 may enter type II alveolar epithelial cells (AECs) through angiotensin-converting enzyme 2 (ACE2) present on the membrane of type II AECs and employs serine protease TMPRSS2 for priming (7). Once type II AECs are infected, they provoke an innate immune response and synthesize type I interferon (IFNα/β), type II IFN (IFNγ), IL-6, and IL-8 (8). In the majority of patients with this response, the infection clears. Once the SARS–CoV-2 single-stranded RNA is released inside the type II AECs, it is recognized by Toll-like receptor 7 (TLR-7) and TLR-8. TLR-7 ligation induces signal transduction via the adaptor protein myeloid differentiation factor 88, and the activation leads to synthesis and release of cytokines and chemokines. This may explain the inflammatory and lung symptoms (Figure 1).

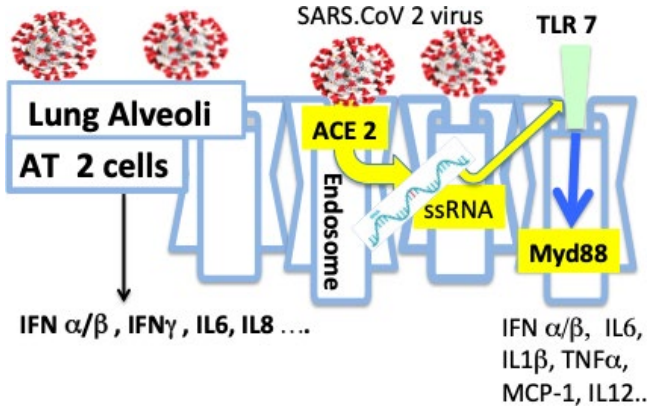

Figure 1. Initial phase of viral infection. In this phase, nonspecific viral agents (while specific agents are awaited), antimalarials, or anti–interleukin-6 (anti–IL-6) (or other anticytokine) agents may be used to shut down the inflammatory process before it evolves into acute respiratory distress syndrome–induced lung failure. SARS–Cov-2 = severe acute respiratory syndrome coronavirus 2; ACE2 = angiotensin-converting enzyme 2; IFNα/β = interferon α/β; TLR-7 = Toll-like receptor 7; ssRNA = single-stranded RNA; AT 2 = type II alveolar epithelial cells; Myd88 = myeloid differentiation factor 88; TNF = tumor necrosis factor; MCP-1 = monocyte chemotactic protein 1.

Treatment that targets the TMPRSS2 protease camostat mesylate, thus inhibiting priming of SARS–Cov-2 spike-S1 protein and its binding to ACE2, may protect against severe outcomes (9). If ACE2 expression is shut down by COVID-19, the inflammation progresses, with release of IL-6 and other cytokines and chemokines. The inflammation may progress to acute respiratory distress syndrome (ARDS) and cytokine storm (1).

RA and SLE have a type I IFN signature (10), which might explain why children and patients with autoimmune diseases may not be affected more severely than the general

population. This is why scientific societies support the idea of continuing treatments (IL-6 inhibitors for juvenile idiopathic arthritis, DMARDs or JAK inhibitors for adult RA, and mycophenolate mofetil or HCQ for SLE). While specific antivirals are awaited, these drugs may help in the hyperinflammatory phase of the infection, and, in fact, several trials are underway using anti–IL-6, other cytokines, or JAK1/2 inhibitors (ClinicalTrials.gov). The key question is whether, or when, to prescribe glucocorticoids, since the American Thoracic Society and Infectious Diseases Society of America (11) did not strongly support the use of glucocorticoids once the hyperinflammatory phase progresses to the cytokine release syndrome and ARDS-like phase. Data from clinical trials and the real world are badly needed to support these theories.

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1. Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, et al. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheumatol 2020;72:1059–63.
2. COVID-19 Global Rheumatology Alliance. URL: https://rheum-ovid.org.
3. Lu X, Zhang L, Du H, Zhang J, Yi YY, Qu J, et al. SARS-CoV-2 infection in children. N Engl J Med 2020;382:1663–5.
4. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like diseases at Italian epicentre of the SARS-CoV2 epidemic: an observational cohort study. Lancet 2020;395:1771–8.
5. Lemaire I, Yang H, Lafont V, Dornand J, Coomes T, Cantin MF. Differential effects of macrophage- and granulocyte-macrophage colony stimulating factors on cytokine gene expression during rat alveolar macrophage differentiation into multinucleated giant cells (MGC): role for IL6 in type 2 MGC formation. J Immunol 1996;157:5118–25.
6. Valiathan R, Ashman M, Asthana D. Effects of ageing on the immune system: infants to elderly. Scand J Immunol 2016;83:255–66.
7. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80.
8. Wang J, Nikrad MP, Phang T, Gao B, Alford T, Ito Y, et al. Innate immune response to influenza A virus in differentiated human alveolar type II cells. Am J Respir Cell Mol Biol 2011;45:582–91.
9. Yale University, sponsor. Camostat mesylate in COVID-19 outpatients. ClinicalTrials.gov identifier: NCT04353284; 2020.
10. De Jong TD, Vosslamber S, Mantel E, de Ridder S, Wesseling JG, van der Pouw Kraan CT, et al. Physiological evidence for diversification of IFNα- and IFNβ-mediated response programs in different autoimmune diseases. Arthritis Res Ther 2016;18:49.
11. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19 infection. Clin Infect Dis 2020;ciaa478.

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Antiphospholipid syndrome is still a rare disease—estimated prevalence in the Piedmont and Aosta Valley regions of northwest Italy: comment on the article by Duarte-García et al

To the Editor:

We read with interest the article by Duarte-García et al (1), in which they reported that the estimated prevalence of antiphospholipid syndrome (APS) was 50 per 100,000 population. APS is an autoimmune disorder characterized by thrombotic events, pregnancy morbidity, or both, in the presence of antiphospholipid antibodies (aPLs) (2). While APS is often thought to be the most common thrombophilia, its global incidence and prevalence in the general population still need to be fully elucidated. Some reports describe an incidence of 5 cases per 100,000 population per year and a prevalence of 40–50 per 100,000 population (1,3–6). In several recent studies, investigators attempted to estimate the prevalence of aPLs in different cohorts, such as in young patients with stroke (7), patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis (4), and patients with a first unprovoked thrombosis (8). To date, APS meets the definition of a rare disease as described by Holué (prevalence ≤5 per 10,000 population) (9).

In order to better estimate the epidemiology of APS, we performed an analysis using a population-based approach, investigating clinicoepidemiologic data on patients with APS in northwest Italy. We collected data from the Piedmont and Aosta Valley Rare Disease Registry, part of the National Registry of Rare Diseases (10). The registry includes demographic, socioeconomic, and disease data, as detailed elsewhere (11) and currently includes 740 patients with a definite diagnosis of APS. The location of the centers reporting APS diagnoses by relative number of diagnoses are depicted in Figure 1. The median age at diagnosis was 45 years (interquartile range 23); 63% of patients were diagnosed at age ≤50 years, 39% at ≤40 years, and 18% at ≤30 years. Taking into account that the population of the Piedmont and Aosta Valley regions is ~4.4 million (12), the estimated prevalence of APS in the region is 1.68 per 10,000 population. The annual incidence from 2010 through 2019 was 1.1 per 100,000 population. APS is considered to be a rare disease according to the Rare Disease Registry of Piedmont and Aosta Valley. Despite the fact that the numbers are relatively small, an accurate estimation of the epidemiology of rare diseases is crucial in order to: 1) plan adequate strategies to maximize