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.

inplantation.[7] Future studies should evaluate these and other clinically relevant outcome measures, such as disturbed myocardial function, signs of cardiomyopathy, and pacemaker complications.

We declare no competing interests.

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1 Costedoat-Chalumeau N, Morel N. Surveillance of congenital heart block in highly specialised care—Authors' reply. *Lancet Rheumatol* 2020; **2:** e204–05.
2 Sonesson SE, Wahren-Herlenius M. Surveillance of congenital heart block in highly specialised care. *Lancet Rheumatol* 2020; **2:** e203–04.
3 Morel N, Lévesque K, Maltret A, et al. Incidence, risk factors, and mortality of neonatal and late-onset dilated cardiomyopathy associated with cardiac neonatal lupus. *Int J Cardiol* 2017; **248:** 263–69.
4 Izmirly, PM, Saxena, A, Kim, MY, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. *Circulation* 2011; **124:** 1927–35.
5 Levesque, K, Morel, N, Maltret, A, et al. Description of 214 cases of autoimmune congenital heart block: results of the French neonatal lupus syndrome. *Autoimmun Rev* 2015; **14:** 1154–60.
6 Fredi, M, Andreoli, L, Bacco, B, et al. First report of the Italian registry on immune-mediated congenital heart block (Lu.Ne Registry). *Front Cardiovasc Med* 2019; **6:** 11.
7 Sonesson, SE, Ambrosi, A, Wahren-Herlenius, M. Benefits of fetal echocardiographic surveillance in pregnancies at risk of congenital heart block: single-center study of 212 anti-Ro52-positive pregnancies. *Ultrasound Obstet Gynecol* 2019; **54:** 87–95

Authors' reply

We thank Marie Wahren-Herlenius and Sven-Erik Sonesson for their comments. We acknowledge that in our first Correspondence[1] we should have compared overall mortality in the three studies, and we apologise for this error.[2–5] When we did this comparison, mortality became 3·8% for the Stockholm cohort (one of 26 patients died; a median follow-up 7·5 years [range 1–19])[2] versus 21·4% in the French registry[5] (45 of 210 patients died; median follow-up 7 years [birth to 36 years]) and 17·5% in the US registry[4] (57 of 325 patients died; follow-up period unknown). When we combined the US[4] and French[5] registries (a total of 102 [19%] of 535 patients died) and compare the mortality with the Swedish series the difference is almost statistically significant (p=0·06).[2,4,5]

In the appendix of their Correspondence, Wahren-Herlenius and Sonesson reported that fetuses treated with fluorinated steroids had better outcomes at their centre compared with those reported in the French and Italian registries. However, because all fetuses at their centre were treated with fluorinated steroids, this analysis does not prove the efficacy of fluorinated steroids. The difference in mortality might be because the oldest case in the Stockholm cohort dates back to 2000, compared with 1976 in the French registry (personal communication), 1969 in the Italian registry,[6] and 1963 in the US registry.[4] The difference in mortality might also be attributable to better management in the expert Swedish centre, including for pacemaker implantation. Consistent with this observation, we encourage physicians who are confronted with a case of congenital heart block to refer the pregnant woman to an expert centre, as done in France.

Nevertheless, although management in expert centres is certainly better, we stand by our conclusion that the efficacy of fluorinated steroids is not supported by analysis of the literature, questioning the need for routine screening of pregnant women who test positive for anti-SSA antibodies. We also continue to believe that more research is needed in this area, research that is better done in centres of excellence.

We declare no competing interests.

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1 Costedoat-Chalumeau N, Morel N. Surveillance of congenital heart block in highly specialised care – Authors' reply. *Lancet Rheumatol* 2020; **2:** e204–05.
2 Sonesson S, Wahren-Herlenius M. Surveillance of congenital heart block in highly specialised care. *Lancet Rheumatol* 2020; **2:** e203–04.
3 Morel N, Levesque K, Maltret A, et al. Incidence, risk factors, and mortality of neonatal and late-onset dilated cardiomyopathy associated with cardiac neonatal lupus. *Int J Cardiol* 2017; **248:** 263–69.
4 Izmirly PM, Saxena A, Kim MY, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. *Circulation* 2011; **124:** 1927–35.
5 Levesque K, Morel N, Maltret A, et al. Description of 214 cases of autoimmune congenital heart block: results of the French neonatal lupus syndrome. *Autoimmun Rev* 2015; **14:** 1154–60.
6 Fredi M, Andreoli L, Bacco B, et al. First report of the Italian registry on immune-mediated congenital heart block (Lu.Ne Registry). *Front Cardiovasc Med* 2019; **6:** 11.

B-cell depletion with rituximab in the COVID-19 pandemic: where do we stand?

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The COVID-19 pandemic has presented several challenges due to insufficient evidence to guide clinical practice. Many patients with severe, refractory rheumatic disease (including vasculitis, systemic lupus erythematosus (SLE), and rheumatoid arthritis) depend on B-cell depletion with anti-CD20 monoclonal antibodies, such as rituximab. In the current crisis, some clinicians and patients have elected to delay maintenance rituximab therapy because of perceived safety concerns. Pausing rituximab therapy carries a risk of destabilising disease control and might increase the requirement for corticosteroids, which could ironically worsen outcomes in patients with COVID-19. Initial results from the European League Against Rheumatism COVID-19 registry suggest poor outcomes in patients receiving 10 mg or more prednisolone (n=64), but not

in the small numbers of patients (n=37) treated with rituximab.[1] However, clinical decision making is further complicated by other observations, such as a severe COVID-19 phenotype being reported in a single patient treated with rituximab for antineutrophil cytoplasmic antibody-associated vasculitis.[2] In this Correspondence, we discuss the position of B-cell-mediated adaptive immunity and rituximab therapy in the current pandemic, with regard to both potential safety concerns and, conversely, the potential for rituximab to treat specific COVID-19 complications.

The safety of rituximab in the context of COVID-19 is unclear. B-cell depletion could compromise antiviral immunity, including development of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies, increase the risk of reinfection, and impair vaccine efficacy (once a vaccine becomes available). The potential risks of hypogammaglobulinaemia secondary to rituximab also need consideration, and the results of clinical trials evaluating convalescent serum are awaited. If trials of convalescent serum show benefit, this could be a potential therapeutic option for patients with immunodeficiency (hypogammaglobulinaemia) secondary to rituximab who develop severe COVID-19.

However, we speculate that rituximab might be beneficial for some patients with severe COVID-19 with specific complications. COVID-19-associated thromboses, severe lung pathology, and hyperinflammation contribute to poor outcomes. These manifestations bear some similarities to those observed in rheumatic diseases, such as antiphospholipid syndrome,[3] rheumatic-associated lung disease,[4] and macrophage activation syndrome[5] secondary to SLE, for which B-cell depletion with rituximab has been shown to be effective. Antiphospholipid antibodies have also been reported in COVID-19 patients with thromboses, although it is unclear whether these antibodies are pathogenic in this context,[3] and lung CT features in some patients with COVID-19 resemble those of fibrotic organising pneumonia (eg, similar to anti-MDA5 anti-synthetase syndrome).[4] It is plausible that anti-SARS-Cov-2 antibodies or immune complexes might potentially evoke monocyte or alveolar macrophage activation, thereby contributing to sustained secretion of proinflammatory cytokines and the development of pulmonary disease. Therefore, could adaptive immunity contribute to poor outcomes in COVID-19, signalling a role for rituximab?

Immunomodulation might improve outcomes in patients with COVID-19-associated hyperinflammation.[5] Although rituximab appears to be effective in treatment of hyperinflammation or haemophagocytic lymphohistiocytosis triggered by Epstein-Barr virus, SARS-CoV-2 (unlike Epstein-Barr virus) is not known to reside in B cells. Therefore, acute B-cell depletion would not be appropriate for COVID-19-associated hyperinflammation. However, rituximab might be useful in specific scenarios in patients with COVID-19 to target chronic adaptive host immune responses. For example, when thrombotic or inflammatory lung complications persist beyond acute infection, and when viral loads are negative or low and anti-SARS-CoV-2 antibodies are positive.

In the context of COVID-19, we call for dedicated research regarding B-cell depletion to better understand the effect and timing of rituximab on patient outcomes and to explore its potential therapeutic use in the management of specific complications of COVID-19, to determine whether judicious use of rituximab might have a role in the pandemic.

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1 Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020; **79:** 859–66.

2 Guilpain P, Le Bihan C, Foulongne V, et al. Rituximab for granulomatosis with polyangiitis in the pandemic of covid-19: lessons from a case with severe pneumonia. *Ann Rheum Dis* 2020; published online April 20. https://doi.org.10.1136/annrheumdis-2020-217549.

3 Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med* 2020; **382:** e38.

4 Giannini M, Ohana M, Nespola B, Zanframundo G, Geny B, Meyer A. Similarities between COVID-19 and anti-MDA5 syndrome: what can we learn for better care? *Eur Respir J* 2020; published online July 6. https://doi.org.10.1183/13993003.01618-2020.

5 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395:** 1033–34.