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.

Notably, concerns have been raised about the suitability and performance of using the mRSS as the primary measure of treatment efficacy in clinical trials of systemic sclerosis, including early diffuse cutaneous disease. Furthermore, Ebata and colleagues[3] did not find that rituximab improved function compared with placebo as assessed by either the health assessment questionnaire disability index (HAQ-DI) or 36-item short-form general health survey (SF-36). However, the baseline mean HAQ-DI was 0·34, which is considerably lower than in previous clinical trials. The authors highlight in their discussion that the HAQ-DI in Japanese patients with systemic sclerosis has been reported to be lower than that of patients in the USA or Europe.[3] The American College of Rheumatology composite response index in diffuse cutaneous systemic sclerosis (ACR CRISS) was developed to assess changes in global disease and is more sensitive than the mRSS to detect treatment differences in clinical trials.

The DESIRES trial is timely and informative, providing further evidence to support treatment with rituximab for patients with systemic sclerosis. However, further research is required, including investigation in an international randomised controlled trial, before rituximab can be considered as a standard of care. The study highlights some of the many challenges that exist in clinical trials for systemic sclerosis. Substantial international collaborative work is progressing to facilitate the next generation of systemic sclerosis clinical trials, including improved patient selection and endpoints.

MH reports personal fees from Actelion Pharmaceuticals, Eli Lilly, and Pfizer, outside of the submitted work. DK reports personal fees from Acceleron, Abbvie, Bayer, Boehringer Ingelheim, CSL Behring, Chemomab, Corbus, Galapagos, Genentech Roche, Horizon Mitsubishi Tanabe, and Prometheus, during the conduct of the study; and has stocks in Eicos Sciences, outside of the submitted work.

*Michael Hughes, *Dinesh Khanna*
khannad@med.umich.edu

Tameside Hospital, Tameside and Glossop Integrated NHS Foundation Trust, Ashton-under-Lyne, UK (MH); Scleroderma Programme, Division of Rheumatology, University of Michigan, Ann Arbor, MI 48109, USA (DK)

1 Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017; **390:** 1685–99.
2 Hughes M, Denton CP, Khanna D. Rituximab for the treatment of systemic sclerosis-interstitial lung disease. *Rheumatology (Oxford)* 2021; **60:** 489–91.
3 Ebata S, Yoshizaki A, Oba K, et al. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): a double-blind, investigator-initiated, randomised, placebo-controlled trial. *Lancet Rheumatol* 2021; published online May 26. https://doi.org/10.1016/S2665-9913(21)00107-7.
4 Khanna D, Clements PJ, Volkmann ER, et al. Minimal clinically important differences for the modified Rodnan Skin Score: results from the Scleroderma Lung Studies (SLS-I and SLS-II). *Arthritis Res Ther* 2019; **21:** 23.
5 Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet* 2016; **387:** 2630–40.
6 Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019; **380:** 2518–28.
7 Khanna D, Allanore Y, Denton CP, et al. Riociguat in patients with early diffuse cutaneous systemic sclerosis (RISE-SSc): randomised, double-blind, placebo-controlled multicentre trial. *Ann Rheum Dis* 2020; **79:** 618–25.
8 Roofeh D, Lescoat A, Khanna D. Emerging drugs for the treatment of scleroderma: a review of recent phase 2 and 3 trials. *Expert Opin Emerg Drugs* 2020; **25:** 455–66.
9 Allanore Y, Wung P, Soubrane C, et al. A randomised, double-blind, placebo-controlled, 24-week, phase II, proof-of-concept study of romilkimab (SAR156597) in early diffuse cutaneous systemic sclerosis. *Ann Rheum Dis* 2020; **79:** 1600–07.
10 Khanna D, Spino C, Johnson S, et al. Abatacept in early diffuse cutaneous systemic sclerosis: results of a phase II investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial. *Arthritis Rheumatol* 2020; **72:** 125–36.
11 Corbus Pharmaceuticals. Corbus Pharmaceuticals presents additional data from RESOLVE-1 study in systemic sclerosis. Nov 9, 2020. https://www.corbuspharma.com/press-releases/detail/347/corbus-pharmaceuticals-presents-additional-data-from (accessed May 18, 2021).

Non-steroidal anti-inflammatory drug use in COVID-19

Published **Online**
May 7, 2021
https://doi.org/10.1016/S2665-9913(21)00144-2

See **Articles** page e498

Early in the COVID-19 pandemic, there was concern in the media that the use of non-steroidal anti-inflammatory drugs (NSAIDs), particularly ibuprofen, might exacerbate COVID-19 symptoms. These concerns, based on unpublished data, led to advice against the use of NSAIDs.[1] Given the widespread general use of NSAIDs, this debate spurred multiple studies to refute or confirm a possible association. The mechanism through which NSAIDs could theoretically be of harm in patients with COVID-19 is by upregulation of angiotensin-converting enzyme 2 (ACE2) receptors in the lungs, arteries, heart, kidney, and intestines,[2] which is used by SARS-CoV-2 as an entry point into cells. Additionally, NSAIDs might delay diagnosis of COVID-19 by masking inflammation and fever. After several initial studies, WHO, the European Medicines Agency (EMA), and the US Food and Drug Administration (FDA) did not advocate against ibuprofen use for COVID-19, but they continue to recommend careful monitoring given the theoretical risk. In *The Lancet Rheumatology*, Thomas Drake and colleagues[3] try to settle the uncertainty.

Drake and colleagues[3] used data from the ISARIC Clinical Characterisation Protocol UK cohort, allowing access to a large number of patients admitted to hospital with COVID-19 (n=72 179; 40 406 [56·2%] of 71 915 were men, 31 509 [43·8%] were women) from

Emmeline Watkins/Science Photo Library

255 UK health-care facilities (representing around 60% of all patients admitted to hospital with COVID-19 in the UK in the study period from Jan 17 to August 10, 2020). The authors analysed the association between NSAID exposure and severe COVID-19 outcomes, including mortality, critical care admission, need for invasive ventilation, need for oxygen, and acute kidney injury. None of these outcomes were significantly associated with NSAID exposure in the 2 weeks before hospital admission. The distribution of previous NSAID use was similar in those who died compared with those who survived, indicating that the association of NSAID use with non-mortality outcomes, including critical care admission and treatments, were not affected by excess mortality in any exposure group. An important subanalysis of the type of NSAID used also did not indicate any increased risk of mortality in patients taking ibuprofen compared with those not taking any NSAIDs (matched OR 0·90, 95% CI 0·71–1·13; p=0·36) or those taking other NSAIDs (matched OR 0·82, 0·66–1·03; p=0·082). As in other similar studies, the authors were unable to provide data on the effect of whether NSAIDs were continued or discontinued during hospital stay. Data on dosages and treatment duration were also not available. Consequently, it is unclear whether a potential harmful effect of NSAIDs is masked by discontinuation during hospital stay, low dosages, or short treatment duration. This study also did not provide any insight into whether comparator drugs (ie, paracetamol) were better, equal, or worse in terms of COVID-19 outcomes. This issue, as well as the effects of taking NSAIDs on acquiring SARS-CoV-2 in the community, has been studied in patients with osteoarthritis; patients were treated with co-codamol (paracetamol and codeine) or co-dydramol (paracetamol and dihydrocodeine) as alternatives to NSAIDs.[4] In support of the current study findings, no indication of harm caused by NSAIDs were seen in this previous study.[4] Another study also confirmed no increased risk of poorer COVID-19 outcomes for NSAID users compared with paracetamol use or no antipyretic drug use.[5] In a subgroup analysis in this smaller study of 403 patients with COVID-19, antipyretic drug use throughout the disease period was reported in 134 patients, of whom 85 were treated with paracetamol and 49 with ibuprofen, and no differential risk of poorer outcomes was apparent for either of the two treatment groups.

In conclusion, NSAID use with COVID-19 appears to confer no increased risk of poorer outcomes. This idea is supported by a growing body of evidence, of which the majority points towards the same conclusion.[4–9] Details regarding use of NSAIDs, including the effects of continuation or discontinuation after hospital admission, dosage, and treatment duration, deserve attention in future studies. The clinical statements from the WHO, EMA, and FDA of lack of harmful effects of NSAID use in COVID-19 infection are supported by the current study. The current study complements several previous observational studies, of which most have supported the lack of association between NSAID use and COVID-19 severity. Ultimately, based on current knowledge, clinicians should not refrain from or discontinue NSAIDs in patients with COVID-19 if NSAID treatment is indicated.

KK reports research grants from The Laerdal Foundation and speaker's honoraria from Novartis, both unrelated to the current Comment. All other authors declare no competing interests.

*Kristian Kragholm, Christian Torp-Pedersen, Emil Fosbol
kdks@rn.dk

Department of Cardiology and Unit of Clinical Biostatistics and Epidemiology, Aalborg University Hospital, 9000 Aalborg, Denmark (KK); Department of Cardiology, Nordsjaellands Hospital, Hillerød, Denmark (CT-P); Department of Cardiology, Rigshospitalet, Copenhagen, Denmark (EF)

1 Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. *BMJ* 2020; **368:** m1086.
2 Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005; **11:** 875–79.
3 Drake TM, Fairfield CJ, Pius R, et al. Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort: a matched, prospective cohort study. *Lancet Rheumatol* 2021; published online May 7. https://doi.org/10.1016/S2665-9913(21)00104-1.
4 Chandan JS, Zemedikun DT, Thayakaran R, et al. Non-steroidal anti-inflammatory drugs and susceptibility to COVID-19. *Arthritis Rheumatol* 2021; **73:** 731–39.
5 Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. *Clin Microbiol Infect* 2020; **26:** 1259.
6 Kragholm K, Gerds TA, Fosbøl E, et al. Association between prescribed ibuprofen and severe COVID-19 infection: a nationwide register-based cohort study. *Clin Transl Sci* 2020; **13:** 1103–07.
7 Abu Esba LC, Alqahtani RA, Thomas A, Shamas N, Alswaidan L, Mardawi G. Ibuprofen and NSAID use in COVID-19 infected patients is not associated with worse outcomes: a prospective cohort study. *Infect Dis Ther* 2021; **10:** 253–68.
8 Bruce E, Barlow-Pay F, Short R, et al. Prior routine use of non-steroidal anti-inflammatory drugs (NSAIDs) and important outcomes in hospitalised patients with COVID-19. *J Clin Med* 2020; **9:** 2586.
9 Jeong HE, Lee H, Shin HJ, Choe YJ, Filion KB, Shin JY. Association between NSAIDs use and adverse clinical outcomes among adults hospitalized with COVID-19 in South Korea: a nationwide study. *Clin Infect Dis* 2020; published online July 27. https://doi.org/10.1093/cid/ciaa1056.