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.

same time. In consequence, 4003 patient volunteers were unavailable to participate in the development of any alternative treatments for SLE; a disease which, despite the success of belimumab, is in dire need of more options.[11]

In a world where recruitment of appropriate volunteers with SLE from trained trial sites is difficult at best, was this huge government-mandated trial absolutely necessary? Why was due diligence through a usual pharmacovigilance system and the continuing acquisition of systematic data from phase 3 studies considered inadequate? Why was the initial dissemination of belimumab, with its established safety profile, saddled with far more phase 4 requirements than are required for most other recently approved treatments?

Compared to SLE study populations, most other study populations include fewer patients who are female and of minority descent. Most other diseases are also not bereft of approved, safe, and effective treatments. The FDA has not provided a coherent justification for diverting so many members of a potential SLE trial population to obtain so much redundant safety data. It seems likely that the heavy phase 4 requirements levied on belimumab could tip the balance of pros and cons faced by treatment developers when considering whether to engage in new high-risk projects for SLE. Hopefully, no such unexplained requirements will be demanded of the next promising candidate for this under-resourced disease.

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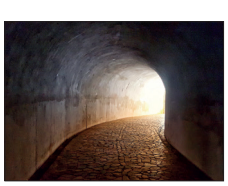
Changing COVID-19 outcomes in patients with rheumatic disease—are we really getting better at this?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See **Articles** page e131

The COVID-19 pandemic has continued to impact the world, and we are now on track to exceed two million deaths worldwide. Patients with rheumatic disease were an immediate concern, but research to date has not convincingly suggested that having a rheumatic disease per se increases the risk of poor outcomes. Instead, poor outcomes seem to be driven by comorbidities and certain medications, such as chronic glucocorticoids and rituximab.[1,2]

An important question to ask is whether we are getting better at treating COVID-19. In *The Lancet Rheumatology*, April Jorge and colleagues[3] address this by exploring temporal trends in patients with rheumatic disease, comparing an early cohort (Jan 20 to April 19, 2020) with a late cohort (April 20 to July 19, 2020). They used a large network of hospitals and health systems across the USA from the TriNetX database with over 8500 patients with rheumatic disease, and completed both an unmatched and matched analysis to try to reduce confounding factors. They found that the risk of hospitalisation for COVID-19 decreased in the late cohort compared with the early cohort (874 [32·4%] of 2701 patients *vs* 1227 [45·4%] of 2701 patients; relative risk [RR] 0·71, 95% CI 0·67–0·76). Outcomes such as intensive care unit

admission, mechanical ventilation, kidney injury, and death were also reduced in the late cohort compared with the early cohort. Among those patients that were hospitalised for COVID-19, the risks of intensive care unit admission, mechanical ventilation, and death were lower in the later part of the pandemic compared with the earlier part of the pandemic (334 [30·7%] of 1089 patients *vs* 450 [41·3%] of 1089 patients; RR 0·74, 95% CI 0·67–0·83). These improvements mirror recent findings within the general population, with reductions in COVID-19 mortality during the later months of the pandemic compared with the first few months.[4] The strengths of this study include its large sample size and detailed patient information, including comorbidities.[3] The authors also did appropriate sensitivity analyses, such as restricting analyses to hospitalised patients and accounting for a washout period.

What are some of the potential explanations for these findings? First, artefacts should be considered, such as expanded testing capacity detecting milder cases in the later months of the pandemic. There is also the potential for factors that were not captured in the analysis, such as background glucocorticoid dose and rheumatic disease severity and activity being unbalanced between the early period and the later period, to bias the outcomes. Additionally, it has been shown that those infected in the later part of the pandemic had a different risk profile, leading to differing background risks of poor outcomes.[5] Insufficient information about outcomes across facilities and geographies, which were not included in propensity score matching, raises the issue of health-care facility differences driven by resource availability or hospital overload. For example, hospitals that were overwhelmed at the start of the pandemic in April might have lowered their threshold for hospitalisation in June as a result of increased bed capacity. By not adjusting for such features, the findings might be explained by these epidemiological and health-care system factors.[6]

Therapeutics have also changed over the course of the COVID-19 pandemic, with treatments being used in the later cohort that were not routinely used in the earlier cohort. Agents such as remdesivir and glucocorticoids have become the standard of care in many health-care settings and, as Jorge and colleagues[3] have pointed out, non-pharmacological treatment has also changed, including avoidance of mechanical ventilation in favour of non-invasive ventilation,[7] altering ventilation strategies,[8] prone positioning,[9] and anticoagulation treatment.[10] It is unlikely that our acquired knowledge of specific risks in patients with rheumatic disease affected results, as comorbidities and therapies such as glucocorticoids and rituximab are difficult to alter in the short term, and in the absence of active infection the recommendations have been to not alter therapy. Therefore, clinical improvements in the treatment of COVID-19 might explain the differences in outcomes over time.

It is difficult to determine how much of the improvement seen in Jorge and colleagues' study is due to clinical factors, such as therapies and practices, versus a selection bias of patients in earlier cohorts compared with later cohorts. A key finding of this study is that use of historical controls might overestimate the effect of treatments. As the pandemic evolves and we continue to measure patient outcomes, it will be important to appropriately account for changes over time and place in longitudinal studies. So, on one hand we must remain vigilant to consider the limitations of outcome studies published during the pandemic, but on the other hand, be hopeful that we are making progress.

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Is chronic non-infectious osteomyelitis with mandibular involvement a distinct disease?

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Chronic non-infectious osteomyelitis is an autoinflammatory bone disorder that can affect patients' quality of life and psychosocial development.[1,2] The disease shows substantial variation in its presentation, with a proportion of patients having monofocal disease, whereas others present with multifocal, frequently symmetrical, bone involvement.[3] Mandibular involvement in chronic non-infectious osteomyelitis is relatively uncommon; it is reported in 2–5% of patients with this disease, and usually presents with jaw pain or swelling.[1–3] Mandibular involvement is also described in the literature as diffuse sclerosing osteomyelitis of the mandible, or Garré's osteomyelitis.[4]

We did a retrospective study of patients with chronic non-infectious osteomyelitis (aged younger than 18 years at diagnosis) with mandibular involvement, who were diagnosed and treated between Jan 1, 2008, and Feb 28, 2020, at four tertiary centres (Bristol and Liverpool, UK; Dresden, Germany; and Dublin, Ireland), to examine challenges associated with this subtype of disease. Clinical outcomes were compared with a subcohort of patients with chronic non-infectious osteomyelitis without mandibular involvement (n=98), from Bristol, where a database of patients is maintained.

17 (6%) of 299 patients with chronic non-infectious osteomyelitis had mandibular involvement (six of 104 from Bristol, four of 64 from Liverpool, three of 71 from Dresden, and four of 60 from Dublin). 14 (82%) of these 17 patients presented with mandibular pain or swelling. Key results are shown in the appendix.

See Online for appendix

Patients with mandibular involvement more frequently had monofocal disease (11 [65%] of 17 patients with mandibular involvement *vs* ten [10%] of 98 patients without mandibular involvement; p<0·0001). A 2020 study from North America reported an even higher proportion of monofocal mandibular lesions (18 [82%] of 22 patients).[5] As monofocal disease requires thorough clinical workup and exclusion of other diagnoses, particularly infectious osteomyelitis and malignancy, the proportion of bone biopsies was significantly higher in the chronic non-infectious osteomyelitis cohort with mandibular involvement (15 [88%] of 17 patients *vs* 52 [53%] of 98 patients; p=0·0066), which is consistent with other published studies (22 [100%] of 22 patients and 17 [77%] of 22 patients).[4,5] Two (12%) of 17 patients with mandibular involvement did not require biopsy, due to reassuring findings on MRI (such as multifocal disease). Three (18%) of 17 patients had bacterial growth identified from the bone biopsy, which had been treated with antibiotics. Several of the biopsies in this study were completed via the intraoral route, which could explain the higher rates of positive cultures in this cohort, compared with those without mandibular involvement (three [18%] of 17 patients *vs* five [5%] of 98 patients). The combination of the organisms grown and the absence of sustained treatment response to antibiotics resulted in the conclusion that these bacteria were a contaminant.

Notably, diagnostic strategies and imaging varied between patients and centres. CTs and MRIs were done more frequently per patient in the group of chronic non-infectious osteomyelitis patients with mandible involvement than in those without. Due to the risks of radiation with CT, as well as the higher sensitivity and ability of MRI to identify multiple bone lesions, MRI is currently considered the most useful radiological tool to diagnose chronic non-infectious osteomyelitis.[6] Several groups have recommended doing a whole-body MRI at diagnosis (also frequently required later in the disease course) to exclude asymptomatic lesions.[2,7,8] The high rates of whole-body MRI scans in patients with mandibular involvement (17 [100%] of 17 patients with mandible involvement had at least one whole-body MRI *vs* 72 [73%] of 98 patients without; p=0·012) might reflect