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Editorial

A deeper dive into rare autoimmune diseases, death and COVID-19 in the first wave of the pandemic

This editorial refers to 'COVID-19 infection, admission and death among people with rare autoimmune rheumatic disease in England: results from the RECORDER project', by Megan Rutter et al., 2022;61:3161–3171.

In this edition of the *Rheumatology* [1], Rutter *et al.* expand on their work reported earlier [2] showing an increase in mortality from all causes in the first wave of the coronavirus disease 2019 (COVID-19) pandemic. What was not clear was whether this increase was due to the rare disease itself, the treatment of the rare disease or COVID-19 itself. Here they show further work from the same cohort in more detail.

The study uses a unique register of a register of complex rare diseases exemplars in rheumatology (RECORDER). This database has a large number of subjects ($n = 168\,680$); 118 374 (70.2%) were female, approximately a quarter (24.5%) had SLE, 22.5% had GCA and 12.6% had JIA, with other rarer diseases making up the balance. This was linked with hospital episode statistics and mortality with cause of death recorded in a standardized format. Some 1874 (1.11%) contracted COVID-19 during the first wave and a surprisingly high proportion (713; 38%) had COVID-19 on their death certificate, giving an age- and sex-standardized mortality of 2.41 (95% CI 2.30, 2.53) *vs* the general population; they also found an age-standardized infection rate of 1.54% (95% CI 1.50, 1.59).

The only disease in the cohort to have specifically less risk of death was GCA, and it was argued that the duration of immune suppression would be shorter in this cohort, although putting all those diseases together is fraught with a lot of assumptions. Firstly, are all rare diseases the same, epidemiologically and immunologically? If one assumes this is an effect of treatment, not all the diseases reported are treated in the same way, and the only disease that is only treated with steroids (GCA) actually shows a reduced mortality. The proportion of patients with GCA was 22.5%, comprising 38 014 patients, second only to SLE with 41 261 (24.5%). The standardized mortality ratio was 0.66 (95% CI 0.60, 0.74) compared with 1.13 (95% CI 0.89, 1.44) for lupus, with 269 and 113 events, respectively. Interestingly, unspecified arteritis had a hazard ratio of 1.50 (95% CI 1.12, 2.02) with 17 632 subjects and 121 events. All other diseases had hazard ratios that crossed 1. This could imply that the pathological process in GCA could be different.

The first question as to whether this cohort is at a high risk was confirmed, and that not only infection but also death and mention of COVID-19 in the death certificate is high. It confirms data from smaller country-wide studies with smaller denominations, like Denmark [3].

This contrasts with data from other national [4] and international registries [5], but this could reflect the methodological issues in those registries as a lot of them depend on physician registration or patient self-report, with a risk of bias.

There are many unknowns in this field, and that is the confounding effect of treatment as it will confound by indication; we are also not aware of whether public health policies in UK like 'shielding' were not effective, as we cannot surmise what the infection rates would have been like if those measures were not implemented.

Additionally, these are data from the first cohort and therefore data on the different COVID-19 variants, such as the delta variant, are not there, and lastly the effect of vaccination in narrowing the odds of infection are not known. We will doubtless be having more national linking data from this and other cohorts going forward, but it would seem that a lot of diseases that are treated by rheumatologists will need to be treated cautiously in case of another epidemic.

GCA could be argued to be a less antibody-driven disease than the others, and this could possibly explain the effect, but unspecified arteritis would have been assumed to have a lower rather than a higher risk as there was no measured antibody. This could be because we still have auto-antibodies to discover in this group, or it could be that the disease is different from GCA fundamentally.

A late complication of GCA includes aneurysmal change; this could have skewed the mortality as they might have had an earlier drop off due to rupture, however this could probably be argued to push the estimate above one rather than below one.

In summary, patients with rare autoimmune diseases had a higher risk of COVID-19 infection and more than twice the risk of death in all but the GCA population; this is interesting, but we await replication of this result in other cohorts.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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