COVID-19 and autoimmune disease - incidence, complications and risk factors: A review of observational studies

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Introduction

Several observational studies of Coronavirus disease 2019 (COVID-19) in autoimmune disease have been published over the past two months. This review will highlight some important findings.

Methods

A MEDLINE search based on Medical Subject Headings (MeSH) terms for autoimmune diseases and COVID-19 was done. This utilised terms for multiple individual autoimmune diseases and synonyms for COVID-19 to capture references that have not yet been indexed according to MeSH terms. Google scholar and https://www.medrxiv.org/ (a preprint server) were also used to find additional manuscripts. Titles, abstracts or full text versions of the papers were reviewed as was necessary. References of selected papers were reviewed for additional studies. Studies were included if they described a population with autoimmune disease and COVID-19 was present or was an outcome.

Results and Discussion

The MEDLINE search yielded 173 results. Additional studies were found via the above methods. 21 were observational studies of COVID-19 in autoimmune disease and were assessed as part of this review.

What is the likelihood of autoimmune patients contracting COVID?

Several cross sectional surveys, mostly from Spain and Italy, have been reported.[1–6] These range in size from 62 to 959 patients. Surveys were carried out in clinic or by phone. Most examined patients with a variety of autoimmune rheumatic conditions, while two focused on SLE and one on large vessel vasculitis.

In these cross sectional surveys, the cumulative incidence of COVID-19 based on microbiological testing varied from 0.2% to 2.8%. Most studies did not report a control population, but in two studies that did there was not an obvious difference in rates of COVID-19 compared to controls[1,2]. Rates of disease based on symptoms, as well as testing, ranged from 2.5% to 13%.

Survival bias must be considered a potential source of weakness of these studies. It was not clear that the investigators would always capture information about patients if they were unwell, admitted to hospital or deceased.

Pablos and colleagues carried out a retrospective cohort study examining a large region surrounding Madrid, Spain. They compared over 26,000 patients with autoimmune rheumatic conditions to a reference population of 2.9 million individuals. The incidence of COVID-19 in autoimmune patients varied by area from 0.23% to 1.24%, but was remarkably similar to control at 0.23% to 1.16%.[7]. Another study from Madrid, which presumably included some of the same patients described a higher incidence of 1.36%.[8] Similarly,

Quartuccio and colleagues found that there was no obvious difference in prevalence when comparing 1051 individuals with autoimmune rheumatic conditions to the general population.[9] An Italian study of all 1195 patients in the Reggio Emilia region taking DMARDs (conventional, targeted synthetic and biological DMARDs) compared this group to the rest of the population of Reggio Emilia. Once adjusted for age and sex, DMARD treated patients were no more likely than control to have a swab taken for COVID-19, to test positive or to be hospitalised.[10]

Do patients with autoimmune disease have different rates of complications?

The largest cohort study globally of a general population is OpenSAFELY. This collaboration between the University of Oxford, NHS England and other academic centers evaluated over 17 million individuals in England via GP electronic health records. This data was linked to hospital COVID -19 deaths. The data included almost 900 000 patients with autoimmune disease: rheumatoid arthritis, lupus or psoriasis. The fully adjusted multivariate model found a hazard ratio (HR) of 1.23 (95% CI 1.12-1.35) for COVID-19 related death for individuals with these autoimmune diseases. 'Other immunosuppressive conditions' numbered 280 000 and carried an even higher risk with HR 1.69 (95% CI 1.21-2.34). Other immunosuppressive conditions included a condition resulting in permanent immunodeficiency such as HIV and aplastic anaemia or temporary immunodeficiency recorded within the previous year.[11]

A study by Ye and colleagues examining a population in China showed a potentially concerning feature of a higher incidence of respiratory failure at 38% in the rheumatic patient group compared to 10% in the non-rheumatic group ($p < 0.001$).However this study had a small sample size, with 21 in the rheumatic group, therefore this result could be spurious. No difference was apparent regarding mortality.[12] A study from Massachusetts of 52 COVID-19 cases in patients with autoimmune rheumatic disease reported that these individuals were more likely to require invasive ventilation (OR 3.2, 95% CI 1.16-8.92). This finding persisted after adjusting for confounders such as comorbidities. Despite this there was no difference in mortality, though the number of events regarding mortality was insufficient to allow inference.[13] Larger studies will be required to confirm if patients with autoimmune rheumatic diseases are more likely to suffer respiratory complications.

What factors are associated with worse outcome?

Arguably the most eagerly anticipated observational study of COVID-19 in autoimmune disease is the report published at the end of May 2020 from the COVID-19 Global Rheumatology Alliance. This described a case series of 600 patients from 40 countries. A large number of these patients were hospitalised (46%) and mortality in this series was substantial at 9%. Note that due to study design, these rates are not generalisable. 71% of the series were female and median age was 46 years. Rheumatoid arthritis, SLE and psoriatic arthritis were the most common diagnoses at 38%, 14% and 12% respectively. 44 patients had vasculitis (7% of cases). The most common comorbidities were hypertension, lung disease and diabetes (33%, 21% and 12% respectively). 85% were on a DMARD and 32% were taking systemic corticosteroids (most less than 10 mg Prednisone equivalent). The majority of cases were from North America and Europe.

On multivariate analysis, corticosteroid at the equivalent of 10mg prednisone or more was associated with a higher odds of hospitalisation (OR 2.05, 95% CI 1.06 - 3.96). Neither DMARD use nor NSAID use were associated with hospitalisation. TNF inhibitor use was associated with a decreased risk of hospitalisation, while there was no demonstrable association with antimalarial use. There was a higher proportion of vasculitis patients in the

hospitalised group (9%) compared to non-hospitalised (5%), but this was not significant on multivariate analysis.[14]

In another cohort from Madrid, being older, male and having comorbidities were risk factors for hospital admission on multivariate analysis. DMARD exposure was not significant.[8] It is important to consider the substantial impact of selection bias in such studies. Cases collated by specialists are more likely to be severe. This limits the generalisability of these studies to all patients with autoimmune disease.

Summary

So far studies suggest that the rates of COVID-19 in individuals with autoimmune disease does not differ to the general population. The largest general population cohort study globally found an adjusted HR of 1.23 for COVID-19 related hospital death in those with autoimmune rheumatic diseases. In the largest case series examining rheumatic disease higher dose corticosteroids were associated with increased odds of hospitalisation. TNF inhibitors were associated with decreased risk. No effect related to hospitalisation was found regarding DMARD, NSAID or antimalarial use.

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