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COVID - how will it continue to change our lives?

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The COVID-19 pandemic has had a profound impact on our health and daily lives. Governments around the world have taken unprecedented actions to deal with this health crisis that rapidly turned into an economic emergency. Although the initial surge in new cases across the globe seems to be behind us, we are still facing the first wave's consequences. COVID-19 continues to be a threat, with an estimated proportion of people infected that never fell below 1.2%. In the UK, this translates to 1 person out of 60 testing positive every day [1]. This is despite over 90% of the UK population having had at least one COVID-19 infection, and 74% of adults having received three vaccine doses, as of April 2022 [2].

The constant viral mutations confer new properties to the virus, potentially increasing its ability to evade existing immune system protections, causing more severe disease, or rendering the virus more transmissible than currently circulating variants. These phenomena are also responsible for re-infections despite previously acquired viral immunity and vaccination. In addition, while many countries have heavily monitored the emergence of new variants during the first waves of the pandemic through widespread community-based PCR testing facilities, the decrease in demand and the cost of these services have led to a drastic reduction in opportunities for monitoring of variants [3].

The COVID-19 pandemic has profoundly transformed the way we deliver healthcare as rheumatologists. From the rheumatology workforce itself, to rheumatology research and training, every aspect of our specialty has had to adapt quickly and often in an unprepared manner. Despite the efforts and remarkable partnership demonstrated by the rheumatology community in its global and integrated approach, the pandemic is likely to have had negative repercussions on patient management and quality of care. A Europe-wide survey gathering the opinions of 1286 rheumatologists from 35 countries revealed that over 80% of respondents cancelled or postponed face-to-face visits with new patients, and 91% did the same for follow-

up visits. Moreover, treatment decisions were frequently postponed and over 70% of respondents were reluctant to start a biological disease modifying anti-rheumatic drug (DMARD)/targeted synthetic DMARD during the pandemic, mainly because of patients' fear, limited availability of screening procedures and decreased availability of rheumatological services. This represents a missed opportunity for optimal patient management [4].

As far as training is concerned, in a survey of over 300 trainees across 33 countries, a negative impact of the pandemic on learning opportunities during rheumatology training, including outpatient clinics (79%), inpatient consultations (59%), didactic teaching (55%), procedures (53%), teaching opportunities (52%) and ultrasonography (36%) was reported. In addition, 39% of trainees reported that COVID-19 negatively affected their ability to continue their pre-pandemic research [5]. Further reports have suggested that the recruitment of participants to non- COVID- 19- related research has been negatively impacted by COVID- 19-related issues including prioritisation of COVID- 19 research, redeployment of research staff and the need for social distancing[6]. Patients' willingness to participate in research during the pandemic has also decreased as stated in a survey of over 1000 individuals living with rheumatic and musculoskeletal diseases (RMDs). Respondents were less inclined to take part in observational or interventional research studies during COVID- 19 compared to before the pandemic (86% vs. 64% and 61% vs. 44% respectively) [7].

Most importantly, the pandemic has had a major impact on people living with RMDs. The first months of the pandemic left many patients with cancelled appointments and unanswered questions, causing intense anxiety and worry in the community. In an online survey of 1800 patients at the beginning of the pandemic, it was found that 58.4% had their rheumatology appointment cancelled and 45.6% reported not having received any information relating to the possible impact of SARS-CoV-2 infection on their rheumatic disease. Additionally, 25%

increased smoking, 18% raised their alcohol consumption, and 46% were unable to continue exercising. Half the patients reported poor well-being, and according to the Hospital Anxiety and Depression Scale (HADS), 58% were at risk of anxiety and 46% of depression [8]. About 50% of patients reported experiencing limitations in the access to rheumatology care, and a similar percentage had changed or discontinued their medications. This issue was also reported for people living with osteoporosis with delays in DXA scanning, interrupted supply of medications and reductions in parenteral medication delivery according to a survey of health professionals across 53 countries [9]. DMARDs shortage and concerns about the increased risk of COVID-19 infection due to immunosuppressive drugs were the most frequently reported reasons for nonadherence. Moreover, the percentage of patients with self-reported uncontrolled disease activity has significantly increased from 8.3% prior to the pandemic to 20% in 2022 [10]. At the beginning of the pandemic, most of the unanswered questions pertained to the risk of infection and severity of disease according to the underlying rheumatic condition and exposure to treatments. While initial reports were scarce and sometimes contradictory, it was impressive to see how the rheumatology community came together in these challenging times and reacted quickly while adhering as far as possible to agreed methodologies and scientific rigour. The COVID-19 Global Rheumatology Alliance is an example of a collegial initiative made up of an international group of rheumatologists, researchers, and patient partners. A registry collating COVID-19 cases among people with RMDs was set up in partnership with the European Alliance of Associations for Rheumatology (EULAR), allowing to analyse COVID outcomes in people with RMDs and factors associated with disease severity and death [11].

Overarching institutions, including EULAR and American College of Rheumatology (ACR) have also offered consistent advice and have provided recommendations on management of RMDs in the context of COVID. At the beginning of the pandemic, the observation of severe

systemic inflammation associated with severe and fatal cases of COVID-19 led to therapeutic agents developed or used frequently in Rheumatology to be at the forefront of experimental therapeutic strategies for COVID-19. In 2020, after carefully reviewing literature published on both COVID-19 pathophysiology and use of immunomodulatory therapies [12,13], EULAR proposed points to consider on the pathophysiology and use of immunomodulatory therapies in COVID-19 [14]; further updated in 2021 [15], to incorporate the most recent evidence from randomized controlled trials.

In parallel, EULAR and ACR were thoroughly monitoring the published literature to regularly update their recommendations on risk and prognosis of SARS-CoV-2 infection as well as safety and efficacy of vaccination against SARS-CoV-2 in patients with RMDs [16]. Although most studies available until then had unclear or high risk of bias, main findings suggested that, in general, the risk of contracting SARS-CoV-2 was not increased in patients with RMDs and overall they were not facing a worse prognosis of COVID-19 than individuals without RMDs. Likewise, no striking differences in risk of developing severe COVID-19 were found between different RMDs. However, there were special cases, and in addition to comorbidities and certain demographic factors already reported in the general population, disease-related factors associated with worse COVID prognosis in patients with RMDs included higher disease activity (with the worse prognosis observed in patients on glucocorticoids possibly being related to confounding by indication), use of rituximab, and possibly the use of Janus kinase inhibitors.

Once vaccination became available, expert groups from various national and international scientific societies provided recommendations on vaccination management for people with RMD [17]. As the first vaccine randomised controlled trials and observational studies were published, these recommendations were quickly supported by scientific evidence [16]. The

main findings suggest that vaccination is generally immunogenic, although antibody responses are lower in people with RMDs than in controls. Vaccine immunogenicity was negatively associated with older age, as well as the use of rituximab and mycophenolate mofetil. While therapeutic recommendations have been variable across countries, the British Society of Rheumatology recommends withholding methotrexate for two weeks around vaccination in patients with stable disease, and the ACR has outlined timings and exceptions for withholding various DMARDs [18]. The Vaccine Response On/Off Methotrexate (VROOM) study has shown that a 2-week interruption in methotrexate treatment enhanced antibody responses after COVID-19 vaccination, at the cost of a mild risk of flare [19]. However, the clinical relevance of this increase in unknown and therefore the potential clinical benefit of this increase is only hypothetical (and needs to be balanced with the possible risk of underlying RMD flare).

With most people who have RMDs having completed at least one full vaccination cycle and a booster, new questions are now arising. For example, it is still unclear how often the general population, let alone people with RMDs and receiving immunosuppressive treatments will need to be revaccinated as there seem to be significant variability in immunogenicity across individuals. As new evidence on this matter accumulates, updates of existing systematic literature reviews will be published, which should help to shed more light on these issues.

Omicron has now become the most prominent variant, leading to less severe infections and resulting in a decrease in COVID-19 public concern. However, the long-term sequelae of acute COVID-19, commonly referred to as long COVID, continue to affect millions of people worldwide. In fact, the number of people experiencing long COVID symptoms is growing, with one in three people in the UK affected [2]. Long COVID, or post-COVID syndrome, is defined by National Institute for Health and Care Excellence (NICE) as symptoms that persist for more than 12 weeks following an infection consistent with COVID-19 and that are not

attributable to an alternative diagnosis [20]. This syndrome typically includes fatigue, myalgia, arthralgia, respiratory symptoms such as breathlessness and cough, tachycardia, sleep disturbance, cognitive impairment and skin rashes. It is still unclear whether post-COVID syndrome is more frequent in people with RMDs and further studies are warranted.

A survey from the Global Rheumatology Alliance found that while most people with RMDs experienced complete symptom resolution within 15 days of COVID-19 onset, about 1 in 4 experienced symptoms for 28 days or longer, and 1 in 10 experienced symptoms for 90 days or longer [21]. Because the symptoms of long COVID can be similar to those of a flare or extra-articular manifestations associated with RMDs, long COVID might be particularly difficult to recognize in the RMD population and may therefore be underestimated. Although most reports currently consist of self-reported symptoms, future studies are needed to assess the frequency of long COVID in the RMD population using standardised definitions, as well as to investigate the possible relationships between RMD type and flare, current immunomodulatory treatments, vaccine doses, and novel viral variants with long COVID.

In summary, as the third year of the pandemic begins, the Rheumatology community has demonstrated an impressive ability to collaborate in a compassionate manner and make every effort not to only maintain the quality of care for people with RMDs but also to reduce the impact on training and research. This has been achieved through the creation of research registries, rigorous review of the available evidence, formulation of recommendations for patient management, and rapid implementation of telehealth and teletraining solutions. Although the prevalence and severity of infection have decreased, it is clear that COVID is still present and here to stay, which poses new challenges for our community, such as designing vaccination schemes beyond the 3rd or 4th booster, identifying risk factors for decreased vaccine effectiveness, and managing post-COVID syndrome in people living with RMDs.

Declaration of interests

PMM has received honoraria from Abbvie, BMS, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche and UCB, all unrelated to this manuscript. None for the other authors.

References

[1] Coronavirus (COVID-19) latest insights - Office for National Statistics n.d. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19latestinsights/infections (accessed February 2, 2023).

[2] The continuing impact of COVID-19 on health and inequalities - The Health Foundation n.d. https://www.health.org.uk/publications/long-reads/the-continuing-impact-of-covid-19-on-health-and-inequalities (accessed February 2, 2023).

[3] Lewis D. The next worrisome coronavirus variant could come from China — will it get detected? Nature 2023;614:15–6.

[4] Dejaco C, Alunno A, Bijlsma JW, Boonen A, Combe B, Finckh A, et al. Influence of COVID-19 pandemic on decisions for the management of people with inflammatory rheumatic and musculoskeletal diseases: a survey among EULAR countries. Ann Rheum Dis 2021;80:518–26.

[5] Young K, Yeoh S-A, Putman M, Sattui S, Conway R, Graef E, et al. The impact of COVID-19 on rheumatology training—results from the COVID-19 Global Rheumatology Alliance trainee survey. Rheumatology Advances in Practice 2022;6:rkac001.

[6] Mitchell EJ, Ahmed K, Breeman S, Cotton S, Constable L, Ferry G, et al. It is unprecedented: trial management during the COVID-19 pandemic and beyond. Trials 2020;21:784.

[7] Mirza M, Siebert S, Pratt A, Insch E, McIntosh F, Paton J, et al. Impact of the COVID-19 pandemic on recruitment to clinical research studies in rheumatology. Musculoskeletal Care 2022;20:209–13.

[8] Garrido-Cumbrera M, Marzo-Ortega H, Christen L, Plazuelo-Ramos P, Webb D, Jacklin C, et al. Assessment of impact of the COVID-19 pandemic from the perspective of patients with rheumatic and musculoskeletal diseases in Europe: results from the REUMAVID study (phase 1). RMD Open 2021;7:e001546.

[9] Fuggle NR, Singer A, Gill C, Patel A, Medeiros A, Mlotek AS, et al. How has COVID-19 affected the treatment of osteoporosis? An IOF-NOF-ESCEO global survey. Osteoporos Int 2021;32:611–7.

[10] Fouad AM, Elotla SF, Elkaraly NE, Mohamed AE. Impact of COVID-19 Pandemic on Patients with Rheumatic and Musculoskeletal Diseases: Disruptions in Care and Self-Reported Outcomes. J Patient Exp 2022;9:23743735221102680.

[11] The COVID-19 Global Rheumatology Alliance | The Global Rheumatology Community's response to the worldwide COVID-19 Pandemic n.d. https://rheum-covid.org/ (accessed February 3, 2023).

[12] Alunno A, Najm A, Mariette X, De Marco G, Emmel J, Mason L, et al. Immunomodulatory therapies for SARS-CoV-2 infection: a systematic literature review to inform EULAR points to consider. Ann Rheum Dis 2021;80:803–15.

[13] Najm A, Alunno A, Mariette X, Terrier B, De Marco G, Emmel J, et al. Pathophysiology of acute respiratory syndrome coronavirus 2 infection: a systematic literature review to inform EULAR points to consider. RMD Open 2021;7:e001549.

[14] Alunno A, Najm A, Machado PM, Bertheussen H, Burmester GR, Carubbi F, et al. EULAR points to consider on pathophysiology and use of immunomodulatory therapies in COVID-19. Ann Rheum Dis 2021;80:698–706.

[15] Alunno A, Najm A, Machado PM, Bertheussen H, Burmester G-RR, Carubbi F, et al. 2021 update of the EULAR points to consider on the use of immunomodulatory therapies in COVID-19. Ann Rheum Dis 2022;81:34–40.
[16] Kroon FPB, Najm A, Alunno A, Schoones JW, Landewé RBM, Machado PM, et al. Risk and prognosis of SARS-CoV-2 infection and vaccination against SARS-CoV-2 in rheumatic and musculoskeletal diseases: a systematic literature review to inform EULAR recommendations. Ann Rheum Dis 2022;81:422–32.
[17] Bijlsma JW, EULAR COVID-19 Task Force. EULAR 2021 updated viewpoints on SARS-CoV-2 vaccination in patients with RMDs: a guidance to answer patients' questions. Ann Rheum Dis 2022;81:786–8.
[18] Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 1. Arthritis Rheumatol 2021;73:1093–107.
[19] Effect of a 2-week interruption in methotrexate treatment versus continued treatment on COVID-19 booster vaccine immunity in adults with inflammatory conditions (VROOM study): a randomised, open label, superiority trial | Elsevier Enhanced Reader n.d. https://doi.org/10.1016/S2213-2600(22)00186-2.
[20] Recommendations | COVID-19 rapid guideline: managing the long-term effects of COVID-19 | Guidance | NICE n.d. https://www.nice.org.uk/guidance/ng188/chapter/Recommendations (accessed February 3, 2023).
[21] DiIorio M, Kennedy K, Liew JW, Putman MS, Sirotich E, Sattui SE, et al. Prolonged COVID-19 symptom duration in people with systemic autoimmune rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. RMD Open 2022;8:e002587.