Trajectories of COVID-19 information in the Annals of the Rheumatic Diseases: the first months of the pandemic

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INTRODUCTION

The COVID-19 pandemic shattered our world, whether at home or in our professional lives. Many of our colleagues or us were in the frontlines. Family and friends turned ill. Meanwhile, researchers all around the world rushed to understand this new disease, evaluate its course and find a cure. As rheumatologists and researchers in rheumatology, we have a deep understanding of the immune system, whether in reaction to an infection or during the course of a rheumatologic disease, and its interplay with the wide range of immunomodulatory treatments available. We also need to understand how this disease impacts our patients. Therefore, since the beginning of the pandemic, the rheumatology community is at the forefront of COVID-19 related research. From the first letter on COVID-19 in March 2020 1 to the end of September, the Annals of the Rheumatic Diseases (ARD) have published more than 200 letters, correspondences, original studies and other articles (figure 1). The first publication on COVID-19 in ARD by Figueroa-Parra et al ‘Are my patients with rheumatic diseases at higher risk of COVID-19?’ already illustrated the most burning questions of the rheumatology community: the potential risks of infection or severe outcome associated with the rheumatic diseases themselves or their therapy and the efficacy of antimalarial drugs in treating COVID-19. 1 Other topics that were widely discussed were the drug shortage of hydroxychloroquine, the use of telemedicine and the effect of the pandemic on patients. In this brief review of ARD publications on COVID-19, we will explore how perceptions and information changed and how interests shifted from one topic to another during the last months.

TYPE OF PUBLICATIONS IN ARD

Most of the publications on COVID-19 from March 2020 to September 2020 on COVID-19 were letters, correspondences and correspondence responses (figure 1). Around half presented original data, mainly in the form of a short correspondence (72%), from which the quality is difficult to assess. The great majority of studies (76%) were only descriptive, and all were observational. Almost half were case reports or case series (47%). The first complete original studies published in extended abstracts or concise reports were published end of May 2020, 1,2,4 and comprised a progressively higher proportion of all the COVID-19 publications the months thereafter, while letters and correspondences decreased (figure 1).

The first recommendations were published in April, with a letter describing the ‘Preliminary recommendations of the German Society of Rheumatology (DGRh eV) for the management of patients with inflammatory rheumatic diseases during the SARS-CoV-2/COVID-19 pandemic’ and a recommendation article for the management of systemic sclerosis: ‘Systemic sclerosis and the COVID-19 pandemic: World Scleroderma Foundation preliminary advice for patient management’. 5,6 The “European League Against Rheumatism (EULAR) provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2” appeared in June. 7 All of these recommendations are provisional, as they were based on the knowledge at the time, and as we will see, this may change swiftly. However, most of the points that were discussed, are still up to date. Update of the EULAR recommendations is planned.

RHEUMATOLOGICAL DISEASES AND THEIR TREATMENTS

The fall from grace of hydroxychloroquine

With their potent in vitro action on coronaviruses and promising results on case series and small trials, antimalarial drugs were the main focus during the first months of the pandemic and promptly discussed as a potential preventive therapy or treatment 8,9 (figure 2A). As we will see later, this will also have an important impact on drug availability for patients with rheumatological diseases. In the first weeks, the positive perception of the therapy is such, that in a study of rheumatology practitioners from India, 67% were more inclined to favour the prescription of antimalarial in their patients. 10 However, others advised to be cautious as rigorous studies were lacking. 11–15 Indeed, from mid-April, the first case series appeared, demonstrating that patients treated for their rheumatological disease with hydroxychloroquine could be infected and present severe outcomes. 14,15 Simultaneously, arrhythmias were described in patients with COVID-19 that could possibly worsen with antimalarial therapy. 16,17 However, some authors argued that the absence of effect of antimalarial therapy could be confounded by the high comorbidity burden and the frequent association with glucocorticoids in infected patients with rheumatological diseases. 15 Yet, further studies in larger cohorts failed to find any differences in the evolution of patients treated with antimalarials or not. 18 In June, reflecting the state of knowledge also outside of the publications in ARD, the...
perspective on antimalarials was shifting, with less and less publications postulating an effect of antimalarial therapy.\textsuperscript{19–21} Indeed, the disinterest in antimalarial therapy as an option in COVID-19 prevention and treatment is mirrored in the decrease in publications on the subject (figure 2A).

**DMARDs: friend or foe?**

Except for antimalarials, which were almost only discussed as a potential treatment, all other treatments were discussed as risk factors and as a potential therapy. Throughout the months, publications were intertwined between manuscripts discussing antirheumatic treatment in patients with rheumatological diseases and patients with non-rheumatological diseases.

None of the other classes of disease-modifying antirheumatic drugs (DMARDs) alone was as much debated as antimalarial therapy. Yet, other DMARDs were discussed from the start (figure 2A). Several small studies did not point to an increased rate of COVID-19 or more severe outcomes with DMARDs, including biological DMARDs (bDMARDs).\textsuperscript{22–26} A study on 600 patients with COVID-19 from the COVID-19 Global Rheumatology Alliance failed to find an increase in the risk of hospitalisation with bDMARDs after adjusting for several confounding factors such as disease activity and comorbidities.\textsuperscript{4} However, describing two fatal cases of COVID-19 under rituximab, Schulze-Koops \textit{et al} advised against a too reassuring and potentially hazardous narrative.\textsuperscript{27} Some authors postulated that low rates of COVID-19 in patients with rheumatological musculoskeletal diseases may rather be associated with protective measures such as social distancing and personal protective equipment, which were adopted by the majority.\textsuperscript{28}

When looking at DMARDs as a treatment, anti-interleukin-6 (anti-IL-6) therapy was one of the first treatment options discussed against the ‘cytokine storm’ of a severe course of COVID-19, beginning with case reports,\textsuperscript{29} small studies,\textsuperscript{30,31} and finally larger observational cohorts with historical or matched comparators, which were among the first studies in the literature comparing IL-6 therapy to standard of care,\textsuperscript{31,32} with promising results. On the other hand, inhibition of IL-6 seemed also to increase the risk of COVID-19 infection and infections in general.\textsuperscript{33,34} Glucocorticoids were alternatively associated with worse\textsuperscript{4,35,36} or improved outcomes,\textsuperscript{37,38} without a clear trend emerging as it appeared to be a risk factor of infection, but clearly beneficial when ventilation was needed. Glucocorticoids are now part of treatment algorithms used in most hospitals. Although one of the most frequent classes of bDMARDs prescribed, only a few articles specifically addressed the potential benefits of tumour necrosis factor-inhibitor therapy.\textsuperscript{39,40} Case series and studies describing a potential advantage of IL-1 inhibition and colchicine were also reported.\textsuperscript{41–44}

In their editorial in August 2020 ‘To immunosuppress: whom, when and how? That is the question with COVID-19’, Winthrop and Mariette expertly summarised the current knowledge on these different therapies. They postulated that some treatments may be deleterious when given too soon and lose their efficacy if given too late, with the current ongoing challenge of finding the potential ‘sweet spot’.\textsuperscript{45} Hopefully, the publication of new criteria defining the ‘cytokine storm’ will help to identify patients that will need specific treatment for this condition.\textsuperscript{46}

**Effect of the rheumatological diseases on COVID-19 infection and its outcome**

Following the trend of antimalarial therapy and COVID-19, systemic lupus erythematosus (SLE) was also one of the ‘hot topics’ of the first months (figure 2B). A letter published beginning of April hypothesised that the absence of cases of infection described in patients with SLE despite thousands of cases

![Figure 1](https://example.com/figure1.png)

**Figure 1** Numbers of publications about COVID-19 from March to September 2020 in the Annals of the Rheumatic Diseases by month and type.

![Figure 2](https://example.com/figure2.png)

**Figure 2** Numbers of publications about COVID-19 in the Annals of the Rheumatic Diseases from March to September 2020 by month and (A) type of treatment and (B) type of disease. SLE, systemic lupus erythematosus.
of COVID-19 could be linked to their treatment with hydroxychloroquine. However, other researchers immediately urged to be cautious with such claims. Indeed, 1 week thereafter, case series presenting the clinical course of COVID-19 in 17 patients with SLE and long-term hydroxychloroquine treatment were described, rapidly followed by a description of larger cohorts of patients with SLE and antimalarial treatment.

Although no single rheumatological disease was as much discussed as SLE (figure 2B), the potential increased risk of COVID-19 infection and severe outcomes with other rheumatological diseases was investigated from the start. The first studies did not report an increase in complications or admission to the intensive care unit. However, later studies, although confirming partially these results, found a higher risk of severe pulmonary disease. Finally, it appeared that maybe distinct types of rheumatological disease may confer different risks, with systemic auto-immune diseases associated with an increased risk of hospitalisation compared with inflammatory arthropathies.

The only consensus that appears to stay throughout the months, when discussing the risk of the diseases themselves or their treatment, is that uncontrolled disease activity should be prevented, as this may increase the risk of infections, and that patients should not stop therapy pre-emptively.

Drug shortage

Due to the enthusiasm of antimalarial therapies in COVID-19, the possibility of drug shortage rapidly became a cause of concern. All around the globe, physicians and patients were confronted with difficulties in accessing antimalarial drugs with as much as 70% of physicians and patients directly concerned. Rheumatologists agreed at this time that, although antimalarial therapy might appear as an option for COVID-19, enough supply for clear and proved indications such as rheumatological diseases should be assured and prioritised. Fortunately, in most countries, measures were rapidly taken at the system level to allocate drug treatment to patients with rheumatological diseases, while waiting for a clear indication of efficacy in COVID-19.

TELEMEDICINE

In line with the ‘stay at home’ advice and because of a lockdown in some countries as well as a focus of the healthcare system on COVID-19 cases, telemedicine rapidly became an invaluable tool and was swiftly implemented in most clinics. Telemedicine seemed to be readily accepted by patients, although older patients or patients with higher disease activity appeared to be less satisfied. Understandably, patients were not in favour of a telemedicine follow-up if they had to come to the clinics for laboratory testing. Rheumatologists also appeared to support telemedicine but expressed that it may not be appropriate for follow-up of active disease in the treat to target era and patients at risk of organ damage. Careful selection of patients who could be followed through telemedicine was thus considered essential.

In addition, as non-specific systemic symptoms are often a hallmark of rheumatic diseases, it was feared that they might be falsely attributed to COVID-19 through telephone triage, impacting speed of diagnosis. Indeed, an increase in the incidence of blindness in giant cell arteritis because of delayed diagnosis was reported. Interestingly, in developing countries, difficulties in implementing telemedicine, when internet access is not always readily available, were as much discussed as the benefits it could provide, when there were no local rheumatologists available.

THE PATIENT’S PERSPECTIVE

A few studies evaluated the impact of COVID-19 on patients with rheumatological diseases, mainly discussing adherence and drug shortage. Although fear of contracting the infection was high, most of the patients perceived the benefit of their medications as superior and only few patients reduced their treatment because of the pandemic, sadly primarily because of drug shortage. Fortunately, this did not seem to have an important impact on disease activity. Patients appeared also to follow preventive measures with as much as 90% of them practising social isolation and/or using personal protective equipment. Regrettably, the social isolation imposed by the pandemic also took a toll on patients’ quality of life with a decrease in both mental and physical components.

CONCLUSION

The publications on COVID-19 in ARD during these last months are representative of the shifting landscape about COVID-19 knowledge, starting with small case reports followed by wider studies giving a much broader and accurate perspective, and the rapid development of provisional recommendations to help manage rheumatological diseases during the pandemic. The scientific methods involve the formulation of hypotheses, based on current knowledge and observation, inductive and deductive reasoning, testing and refining of the hypotheses. Assumptions that appeared promising at first, can be smashed in the process or confirmed. The articles published in ARD are no exceptions, which spreads a reassuring light on the commitment of the rheumatology community to improve scientific knowledge. The profound knowledge that the rheumatological community, including basic researchers, has about the immune system bring rheumatologists at the forefront of the scientific progress in this field. COVID-19 also opened new perspectives in the treatment of patients with telemedicine, their fears, their trust in their therapy and the sobering effect of the endorsement of unfounded therapies on drug supply.

While we face uncertain times ahead, the swift ability to adapt to change of the wide rheumatology community, including patients, researchers and healthcare practitioners, whether in terms of clinical knowledge or clinical practice, is a steady foundation on which we can hope to build a brighter future.

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