

EULAR PROVISIONAL RECOMMENDATIONS FOR THE MANAGEMENT OF RHEUMATIC AND MUSCULOSKELETAL DISEASES IN THE CONTEXT OF SARS-CoV-2

April 2020 version

Robert B.M. Landewé¹, Pedro M. Machado², Féline P.B. Kroon³, Johannes W.J. Bijlsma⁴, Gerd R. Burmester⁵, Loreto Carmona⁶, Bernard Combe⁷, Massimo Gall⁸, Laure Gossec⁹, Annamaria Iagnocco¹⁰, John D. Isaacs¹¹, Xavier Mariette¹², Iain B. McInnes¹³, Ulf Müller-Ladner¹⁴, Peter J.M. Openshaw¹⁵, Giovanni Rezza¹⁶, Josef S. Smolen¹⁷, Tanja Stamm¹⁸, Dieter Wiek¹⁹, Hendrik SchulzeKoops²⁰

¹MD, Professor of Rheumatology; Amsterdam University Medical Center & Zuyderland Medical Center, Heerlen, The Netherlands

²MD; Centre for Rheumatology & Department of Neuromuscular Diseases, University College London, London; Department of Rheumatology, University College London Hospitals NHS Foundation Trust, London; ^{and} Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK.

³MD; Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands & Zuyderland Medical Center, Heerlen, The Netherlands

⁴MD, Professor of Rheumatology; University Medical Center Utrecht, The Netherlands

⁵MD; Department of Rheumatology and Clinical Immunology, Charité – Universitätsmedizin Berlin, Freie Universität und Humboldt-Universität, Berlin, Germany

⁶MD, PhD, Scientific Director; Instituto de Salud Musculoesquelética, Madrid, Spain

⁷ MD, PhD; department of Rheumatology, CHU Montpellier, Montpellier University, Montpellier, France

⁸ MD, Professor of Infectious Diseases; Department of Biomedical and Clinical Sciences L.Sacco, Università di Milano, Infectious diseases unit ASST-FbF-Sacco, Milano, Italy

⁹ MD; Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris & Rheumatology department Pitié-Salpêtrière hospital, AP-HP. Sorbonne Université, Paris, France.

¹⁰ MD, Professor of Rheumatology; Università degli Studi di Torino, Turin, Italy

¹¹ MD; Institute of Translational and Clinical Medicine, Newcastle University and Musculoskeletal Unit, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

¹² Université Paris-Saclay, INSERM, CEA, Centre de recherche en Immunologie des infections virales et des maladies auto-immunes ; AP-HP. Université Paris-Saclay, Hôpital Bicêtre, Rheumatology department, 94270, Le Kremlin Bicêtre, France.

¹³ MD; University of Glasgow, Glasgow, United Kingdom, G128QQ

¹⁴ MD; Justus-Liebig University Giessen, Department of Clinical Rheumatology and Immunology, Campus Kerckhoff, Bad Nauheim, Germany

¹⁵ MD; National Heart & Lung Institute, Imperial College London, UK

¹⁶ MD, Director; Department of infectious diseases, National Institute of Health (ISS), Rome, Italy

¹⁷ MD; Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Austria

¹⁸ PhD; Section for Outcomes Research, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna

¹⁹ EULAR/PARE Patient Research Partner & Deutsche Rheuma-Liga Research Partner

²⁰ MD; Division of Rheumatology and Clinical Immunology, Department of Internal Medicine IV, University of Munich, Munich, Germany

Corresponding author

Robert B.M. Landewé, Amsterdam University Medical Center & Zuyderland Medical Center, location Heerlen, The Netherlands. E-mail { [HYPERLINK ftp://address: landewe@rlandewe.nl](mailto:landewe@rlandewe.nl) }

ABSTRACT

These provisional EULAR-recommendations address several aspects of Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), the virus, and the disease caused by SARS-CoV-2, Coronavirus disease 2019 (COVID-19) and are meant for patients with rheumatic and musculoskeletal diseases (RMD) and their caregivers.

A taskforce of 20 members was convened by EULAR and met several times by videoconferencing in April 2020. The taskforce finally agreed on 5 overarching principles and 13 recommendations covering four generic themes: i) General measures and prevention of SARS-CoV-2 infection; ii) The management of RMD when local measures of social distancing are in effect; iii) The management of COVID-19 in the context of RMD; and iv) The prevention of other infections than SARS-CoV-2. EULAR considers this set of recommendations as a 'living document' and a starting point, which will be updated as soon as promising new developments with potential impact on the care of patients with RMD become available.

INTRODUCTION

These provisional recommendations address several aspects of Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), the virus, and the disease caused by SARS-CoV-2, Coronavirus disease 2019 (COVID-19). They address the implications for patients with rheumatic and musculoskeletal diseases (RMD). They have been commissioned by EULAR, and developed under its auspices, in order to guide both rheumatologists and health professionals in rheumatology (HPR) who care for patients with RMD, COVID-19-treating physicians as well as patients with RMD themselves and their family members.

Many (inter)national professional organizations in rheumatology and beyond, as well as government bodies, have issued guidance documents pertaining to the prevention, diagnosis and treatment of SARS-CoV-2 infection and COVID-19. Since generic recommendations do not focus on patients with RMD and their circumstances, EULAR considered it essential to provide a set of recommendations that are applicable to all rheumatologists and HPRs and their patients with RMD in EULAR-countries. Guidelines issued by national (professional) organizations can occasionally be more or less restrictive than EULAR-recommendations. By no means EULAR intends to overrule existing guidelines at the country-level of EULAR-member states. EULAR only aims to provide a synthesis of the best available aggregated expert opinion to inform rheumatologists and HPR and patients with RMD about management decisions to be taken in the context of the SARS-CoV-19 epidemic.

SARS-CoV-2 is a new virus and COVID-19 a new disease. Scientific knowledge is rapidly accruing, but methodologically robust information from well-controlled trials and experiments is lacking to date. In contrast, we face a flood of unreliable largely uncontrolled studies and even *fake news*. It is to be expected that scientific knowledge of the caliber that EULAR usually requires to design and update their recommendations will be lacking for a while. Nevertheless, people with RMD appropriately confront their rheumatologists and HPR with questions about treatment implications and COVID-19 associated anxiety. In turn, rheumatologists and HPR may feel uncertain about how to advise in the best interest of their patients. Therefore, EULAR decided not to wait until robust scientific knowledge becomes available, but to deviate from their Standard Operating Procedures[1] and to convene a taskforce of international experts to provide provisional guidance for rheumatologists, HPR and patients with RMD. Although the taskforce was hampered by restrictions of social distancing, preventing them to meet in person – it performed the complete process successfully by videoconferences.

EULAR is committed, in contrast to our usual procedures, to consider this set of recommendations as a ‘living document’ and a starting point, which will be updated as soon as promising new developments with potential impact on the care of patients with RMD become available. These developments will be monitored closely, their quality judged by a team of EULAR methodologists and after further discussion in the taskforce included in an updated version of the recommendations when appropriate.

PROCEDURES

Focus of recommendations

These recommendations pertain to the management of patients with RMD insofar as the current SARS-CoV-2 epidemic and its consequent COVID-19 disease may interfere with usual management of patients with RMD. These recommendations are decidedly not focused on the diagnosis or treatment of COVID-19. There is some focus on so-called ‘inflammatory’ RMD, because of specific issues that patients with systemic autoimmune diseases, partly due to their treatments, may face or may have concerns about, without excluding all patients with other types of RMD.

The taskforce composition

This EULAR taskforce consists of 22 experts from 7 EULAR member states. Most experts are internationally recognized rheumatologists and immunologists with many years of clinical and

scientific experience, who fulfil or have fulfilled official positions in the EULAR organization. EULAR's current, past and incoming presidents (HB, IBM, AI, JS), as well as the current, past or incoming chairs of EULAR's standing committees on epidemiology and health services research (PMM, LC, LG), clinical affairs (UML, RL) and investigative rheumatology (XM) are members of the taskforce, among others. The taskforce was supported by an expert on viral lung diseases (PO), an infectious disease specialist (GR), the EULAR vice-president representing health professionals in rheumatology (TS), the EULAR vice-president representing patients with arthritis and rheumatism (PARE) (DW), and a clinical fellow (FK). The taskforce was presided by the past-president of EULAR (JB) and selected an overarching steering committee consisting of three clinically active rheumatologists (RL, PMM, HSK) and one fellow (FK). All taskforce members had ample experience with the development of EULAR recommendations according to EULAR's SOPs.[1]

Handling potential conflict of interest

In accordance with EULAR's SOP, taskforce members are asked on an annual basis to provide and update their interactions with third-parties (guideline-committees, reimbursement bodies, pharmaceutical industries or other industries) that are not directly related to all day patient-care but may give an impression to others of conflict of interest (*potential COI*). The EULAR office keeps record of these declared potential COIs.

The steering committee's workflow

First, the steering committee collected, largely from official websites, existing guidance documents stemming from several European and non-European countries. Some of these focused on RMD and were prepared by national professional organizations of rheumatology (German,[2] French,[3, 4] Spanish[5]) or general medical organizations (United Kingdom National Health Service (NHS),[6] National Institute for Health and Care Excellence (NICE)[7]). Others were generic guidelines, not focusing on RMD (World Health Organization (WHO)[8]). During the process a set of recommendations by the American College of Rheumatology became available.[9]

Thereafter, the steering committee proposed five overarching principles (OP). In EULAR's recommendation documents, OP usually serve to underpin the content of the subsequent recommendations; OP set the stage on which the body of guidance that follows is built. Next, the steering committee distinguished four areas of interest for which recommendations seemed appropriate: i) General measures and prevention of SARS-CoV-2 infection; ii) The management of RMD when local measures of social distancing are in effect; iii) The management of COVID-19 in the context of RMD; and iv) The prevention of other infections than SARS-CoV-2.

In total, the steering committee conceived 14 recommendations (between 2 and 5 per area of interest) that were largely based on existing guidelines and recent personal clinical experience of steering committee members. Explanatory information accompanied each of the proposed OP and recommendations.

The steering committee met three times within a period of ten days by videoconferencing.

The taskforce's workflow

The taskforce members took notice of the draft recommendations by email and were given the opportunity to propose changes, new themes and recommendations. These suggestions were collected by the steering committee and discussed in a taskforce meeting by videoconference (April 14). The steering committee drafted a second proposal, including the proposed changes, and one new recommendation, which was discussed one week later in a second taskforce meeting (April 21). Consensus was reached on April 21, and the steering committee was assigned the task to prepare the manuscript. All taskforce members commented on and agreed to the final version of the manuscript before submission.

Target audience

In line with EULAR's SOP, the taskforce agreed to target their guidance primarily on rheumatologists, HPR and patients with RMD and their families. Secondly, these recommendations target public-health officials and public-health experts by making them aware of particular problems pertaining to patients with RMD and their treatments, as well as policy makers, who decide about measures of social distancing, access to healthcare for patients with RMD and availability of drugs for patients with RMD.

Systematic literature research

It was decided upfront that a systematic literature research to inform the process would not be performed. This is justified on the current absence of sufficient appropriately controlled clinical studies or relevant epidemiologic reports as to inform a meaningful process.

Formal decision-making

A formal voting procedure was not performed. Each expert's level of agreement (from 0 (no agreement at all) to 10 (fully agree)) with the statement was solicited by email for each OP and recommendation on April 23. The mean level of agreement, as well as the proportion of experts with a level of agreement of at least 8, was calculated.

RESULTS

The taskforce finally agreed on 5 OP and 13 recommendations. The bullet-text of these OP and recommendations can be read in Table 1. Below, an item-by-item discussion is outlined, that clarifies the choice of themes and wording and sheds more light on the discussions that have taken place in the taskforce.

Table 1. EULAR provisional recommendations for the management of rheumatic musculoskeletal diseases in the context of SARS-CoV-2 - April 2020 version.

	Overarching principles	LoA	
		mean±SD	≥8/10 (%)
1 .	To date, there is no evidence that patients with RMD face more risk of contracting SARS-CoV-2 than individuals without RMD, nor that they have a worse prognosis when they contract it.	9.1±1.2	84
2 .	The diagnosis and treatment of COVID-19 in patients with RMD is the primary responsibility of an expert in treating COVID-19, such as a pulmonologist, an internist or a specialist in infectious diseases, dependent on local	9.3±1.3	84
3 .	Rheumatologists are the leading experts for the immunosuppressive treatments of their patients and should be involved in the decision to maintain	9.2±2.4	89
4 .	The knowledge about immunosuppressive treatments, including sDMARDs and bDMARDs, for the treatment of severe COVID-19 is rapidly evolving. In view of their expertise, rheumatologists should make themselves available for local-hospital, regional or national guideline committees for COVID-19. The use of immunosuppressive drugs for the treatment of COVID-19 should be a multidisciplinary decision.	9.3±1.4	84
5 .	Availability and distribution of, and access to, sDMARDs and bDMARDs for the treatment of patients with RMD as well as for patients with COVID-19 (but without RMD) is a delicate societal responsibility. Therefore, the off-label use of DMARDs in COVID-19 outside the context of clinical trials	8.9±1.2	89
	Recommendations		
1	Patients with RMD should be strongly advised to comply with all preventive and control measures prescribed by the health authorities in	9.9±0.5	95
2	Patients with RMD should in general be advised to comply with the same preventive and control measures as patients without RMD.	9.3±1.0	89
3	Patients with RMD who do not have suspected or confirmed COVID-19 should be advised to continue their treatment unchanged, namely NSAIDs, glucocorticoids, sDMARDs, bDMARDs, osteoporosis medications and	9.6±0.6	94
4	If the RMD and its drug treatment are stable, and signs or symptoms of drug toxicity are absent, regular blood monitoring and face-to-face rheumatology consultations can be postponed temporarily. If necessary, consultation can	9.6±0.9	94
5	If the RMD is active, if drug therapy has recently been started or needs adjustment, or if signs or symptoms of drug toxicity emerge, patient and rheumatologist should liaise, weigh the risks of a visit to the clinic against the limitations of remote advice, and decide together.	9.7±1.0	89
6	If a patient with RMD is offered an outpatient, day-care or other type of hospital- appointment, patients and members of the rheumatology team should follow local guidance for infection prevention and control, including the use of personal protection equipment if indicated.	9.9±0.2	94
7	Patients with RMD without COVID-19 symptoms who have been in contact with a SARS-CoV-2 positive person should be tested for SARS-CoV-2	8.0±2.5	63
8	If a patient with RMD and symptoms of COVID-19 is chronically treated with glucocorticoids, this treatment should be continued.	8.8±1.6	79
9	If patients with RMD experience mild* symptoms of COVID-19, potential treatment changes in DMARDs should be discussed on a case-by-case basis.	8.9±1.4	84

10	Patients with RMD and initially mild symptoms who experience worsening** of COVID-19 symptoms should immediately seek further health care advice of an expert in treating COVID-19, such as a pulmonologist, an internist or a specialist in infectious diseases, dependent on local circumstances.	9.8±0.5	94
11.	Patients with RMD who are admitted to the hospital because of significant*** COVID19 should follow local treatment recommendations for COVID-19 as applied by the treating expert.	9.7±0.8	89
12.	Patients with RMD without symptoms of COVID-19 should be advised to update their vaccination status in accordance with the EULAR-recommendations for the vaccination of patients with RMD, with a particular focus on pneumococci and Influenza.	9.4±1.0	89
13	In patients with RMD treated with cyclophosphamide or glucocorticoids, pneumocystis Jiroveci pneumonia-prophylaxis should be considered.	9.3±0.9	89

*See definition of mild symptoms in Box 1. **See definition of worsening in Box 1. ***See definition of significant COVID-19 in Box 1. bDMARD, biologic disease modifying anti-rheumatic drug; COVID-19, Coronavirus disease 2019; EULAR, European League Against Rheumatism; LoA, level of agreement; NSAID, non-steroidal anti-inflammatory drug; RMD, rheumatic and musculoskeletal diseases; sDMARD, synthetic disease modifying anti-rheumatic drug; SARS-CoV-2, Severe Acute Respiratory Syndrome coronavirus 2.

Box 1. Symptoms of COVID-19

*Mild symptoms of COVID-19:

These include symptoms of common cold, such as sore throat, running nose, nasal congestion, anosmia or dysgeusia, fatigue, generalized or local myalgia, arthralgia without clinical swelling, anorexia, diarrhoea, as well as temperature elevation (<38C).

**Worsening of mild COVID-19 symptoms:

This applies when a patient with formerly mild symptoms of COVID-19 gets fever ≥38C or subjective shortness of breath or tachypnoea (>20/min) or hypoxia or cyanosis.

***Significant symptoms of COVID-19:

These include all of the above, but accompanied by fever (≥38C) or subjective shortness of breath or tachypnoea (>20/min) or hypoxia or cyanosis.

Box 2. Cytokine release syndrome

Cytokine release syndrome (CRS) (also described as cytokine storm, macrophage activation syndrome [MAS] or secondary haemophagocytic lymphohistocytosis [sHLH]) is an emergency condition of systemic hyperinflammation that may occur in patients with COVID-19 pneumonia.[10] CRS should be suspected in patients with confirmed COVID-19 pneumonia (either by polymerase chain reaction [PCR] testing or by computed tomography [CT]-scan) who rapidly deteriorate and experience respiratory failure. Potential biomarkers of CRS are very high levels of C-reactive protein, D-dimer, ferritin and IL-6 or a high *H Score*, which computes a value based on the following components: temperature, organomegaly, number of cytopenias, triglycerides, fibrinogen, ferritin, aspartate aminotransferase, haemophagocytosis on bone marrow aspirate, and known immunosuppression.[11]

OP 1. To date, there is no evidence that patients with RMD face more risk of contracting SARS-CoV-2 than individuals without RMD, nor that they have a worse prognosis when they contract it.

This OP states that, according to current knowledge, patients with RMD should not be managed differently than individuals without RMD. It is currently unknown whether a specific RMD or treatment with a specific drug influences the risk (increase, decrease or no change in the risk) of developing COVID-19. While many advisories, including official government bodies in some countries,[6, 12-14] postulate an increased risk for patients with inflammatory/autoimmune diseases or those using immunosuppressive drugs, since they extrapolate existing data stemming from registries that such patients have increased risk of some infections,[15-17] it should be stated clearly that such an association for SARS-CoV-2 and COVID-19 has not (yet) been established. From this OP follows that there is no current basis for preventive measures that are more or less restrictive than those issued for the general population (see recommendations 1&2). However, there is also no evidence that patients with RMD, irrespective of their treatment, have a better prognosis than other individuals.

Level of agreement: 9.1 ± 1.2 ; 84% scored 8/10 or higher.

OP 2. The diagnosis and treatment of COVID-19 in patients with RMD is the primary responsibility of an expert in treating COVID-19, such as a pulmonologist, an internist or a specialist in infectious diseases, dependent on local circumstances.

This OP serves to make clear that the diagnosis and treatment of SARS-CoV-2-infection and COVID-19 does not and should not belong to the expertise and responsibility of the rheumatologist or the HPR working in the field of rheumatology. Dependent on local (national) circumstances, several different medical specialists take care of these patients.

Level of agreement: 9.3 ± 1.3 ; 84% scored 8/10 or higher.

OP 3. Rheumatologists are the leading experts for the immunosuppressive treatments of their patients and should be involved in the decision to maintain or discontinue them.

This OP states that the rheumatologist is an important discussion partner in making decisions on drug-treatment in patients with RMD, in particular patients that use synthetic or biologic disease modifying anti-rheumatic drugs (sDMARDs and bDMARDs, respectively) or other drugs that have an immunosuppressive connotation. This OP is important since recent information suggests that clinicians taking care of patients with COVID-19 are tempted to stop all treatments that are believed to be associated with impaired virus-clearance, without considering the risk of a flare of the underlying RMD, leading to unwarranted situations and anxiety in patients. The treating rheumatologist is the pre-eminent discussion partner for experts in treating COVID-19 to decide if a drug for RMD can be paused safely or should be continued (see below).

The rheumatologist's role should not be marginalised.

In the taskforce there was dissent about using the term 'immunosuppressive' vs. the term 'immunomodulatory'. The taskforce finally decided to keep the term 'immunosuppressive', since it is the fear for and perception of inappropriate suppression of the immune system that leads to the discontinuation of these drugs in case of COVID-19. Still, some of them do not formally suppress the immune system (e.g., hydroxychloroquine (HCQ) and sulfasalazine) and bDMARDs that target cytokines specifically block one element of the immune system whilst leaving remaining components unmanipulated.

Level of agreement: 9.2 ± 2.4 ; 89% scored 8/10 or higher.

OP 4. The knowledge about immunosuppressive treatments, including sDMARDs and bDMARDs, for the treatment of severe COVID-19 is rapidly evolving. In view of their expertise, rheumatologists should make themselves available for local-hospital, regional or national guideline committees for COVID-19. The use of immunosuppressive drugs for the treatment of COVID-19 should be a multidisciplinary decision.

This OP further elaborates on OP3, but addresses the matter from a different angle: it acknowledges the practice that some DMARDs (such as (hydroxy)chloroquine) are now, rightly or wrongly, propagated for the prevention or treatment of COVID-19. Several bDMARDs (such as IL-6 and IL-1 inhibitors) and janus kinase inhibitors (JAKi) are under investigation for treating severe COVID-19 and are sporadically used 'off-label', in particular in COVID-19 patients with concomitant cytokine release syndrome (CRS; see Box 2 for an explanation). The IL-6-receptor blocker tocilizumab has been approved by FDA and EMA for patients with CAR-T-cell-treatment associated CRS and recently by Chinese authorities for severe COVID-19.[18] Rheumatologists may possess relevant knowledge about the indications, contraindications and toxicity of DMARDs and cytokine inhibitors and could be consulted by physicians treating patients with COVID-19 and by guideline committees. The term 'multidisciplinary' here refers to different medical specialists, but it is obvious that the decision to start, stop or continue treatment with DMARDs or cytokine inhibitors in the end should be a shared decision between patient and physician(s).

Level of agreement: 9.3 ± 1.4 ; 84% scored 8/10 or higher.

OP 5. Availability and distribution of, and access to, sDMARDs and bDMARDs for the treatment of patients with RMD as well as for patients with COVID-19 (but without RMD) is a delicate societal responsibility. Therefore, the off-label use of DMARDs in COVID-19 outside the context of clinical trials should be discouraged.

This principle elaborates on the potential lack of drug availability for RMD-patients (with or without COVID-19) due to unproven overuse for COVID-19 patients. The best example is the shortage of HCQ for patients with systemic lupus erythematosus, that arose in some countries after rumours that this drug would be effective in COVID-19.[19] Similar concerns exist for particular bDMARDs (e.g., tocilizumab). ‘Delicate responsibility’ refers to the following dilemma: in the absence of a proven treatment for COVID-19, clinicians will understandably try every drug with possible efficacy in critically ill patients, and publish their successes in case-reports. However, by doing so they may unintentionally contribute to creating false hope and conveying wrong information. Since some DMARDs are potentially efficacious in COVID-19, patients with RMD can be affected disproportionately. It is because of this dilemma that off-label medication use outside the context of clinical trials should be discouraged. Physicians that nevertheless decide to treat patients with COVID-19 with DMARDs off-label have a responsibility to document their argumentation and the follow-up of these patients carefully.

Level of agreement: 8.9 ± 1.2 ; 89% scored 8/10 or higher.

General measures and prevention of SARS-CoV-2 infection

Recommendations 1-3 pertain to general public-health measures and precautions. The scope is that of RMD patients who have no signs of COVID-19 and have not been in contact with COVID-19 patients.

RC 1. Patients with RMD should be strongly advised to comply with all preventive and control measures prescribed by the health authorities in their countries.

In line with OP1 to date there is no reason to assume that patients with RMD have a higher risk of being infected with SARS-CoV-2, or fare worse if they get COVID-19. Obviously, this means that currently known risk factors for severe COVID-19, including older age, male gender, comorbid cardiovascular disease and obesity, also pertain to patients with RMD.[20] This recommendation tells patients and their rheumatologist/HPR to behave like all other individuals in society in their attempts to avoid or control infection. We note that some RMD share increased prevalence of some of these co-morbidities especially metabolic syndrome, cardiovascular disease and obesity.

Level of agreement: 9.9 ± 0.5 ; 95% scored 8/10 or higher.

RC 2. Patients with RMD should in general be advised to comply with the same preventive and control measures as patients without RMD. This recommendation reiterates that there is also no reason for patients with RMD to take different

measures, given there is no added risk for them. There is also no reason to believe that patients with RMD have more or less risk than others because of their DMARD use. Level of agreement: 9.3±1.0; 95% scored 8/10 or higher.

RC 3. Patients with RMD who do not have suspected or confirmed COVID-19 should be advised to continue their treatment unchanged, namely NSAIDs, glucocorticoids, sDMARDs, bDMARDs, osteoporosis medications and analgesics, among others.

Based on the same rationale as OP1, it is unadvisable to change chronic treatment for RMD in patients who are not suspected of COVID-19. This recommendation does not only refer to patients with 'inflammatory' RMD, but to all patients with RMD, and serves to reassure those who are concerned about the safety of their drugs with respect to COVID-19.

Level of agreement: 9.6±0.6; 94% scored 8/10 or higher.

Management of the RMD when local measures of social distancing are in effect Recommendations 4-6 advise patients with RMD how to act during or in the aftermath of the SARSCoV 2 epidemic, when official restrictions in the freedom of movement apply. They refer to all potential levels of existing social distancing, varying from, e.g. keeping 1-1.5 or 2-meter distance for subpopulations to a complete country-lockdown.

RC 4. If the RMD and its drug treatment are stable, and signs or symptoms of drug toxicity are absent, regular blood monitoring and face-to-face rheumatology consultations can be postponed temporarily. If necessary, consultation can take place remotely.

This recommendation tells patients with RMD and their caregivers that usual regular monitoring visits can safely be postponed ones or twice (up to 6 months maximum) in patients with stable disease. Instead, patients may communicate with their rheumatologists and HPR via telephone or videoconference. Email communication is generally discouraged, because of issues with privacy protection, unless approved secure email transfer systems are used.

Level of agreement: 9.6±0.9; 94% scored 8/10 or higher.

RC 5. If the RMD is active, if drug therapy has recently been started or needs adjustment, or if signs or symptoms of drug toxicity emerge, patient and rheumatologist should liaise, weigh the risks of a visit to the clinic against the limitations of remote advice, and decide together.

This recommendation clarifies that a visit to a clinic or hospital implies a judgmental trade-off between the risk of advising the patient only remotely and the patient's and rheumatologist/HPR's risk of contracting

SARS-CoV-2 in the hospital or care facility. A generic recommendation (*do's and don'ts*) cannot be formulated, since the outcome of this decision is situational and dependent on the needs of the patient and the appraisal of the physician/HPR. This may particularly be the case as COVID-safe areas of clinics and hospitals are increasingly created.

Level of agreement: 9.7±1.0; 89% scored 8/10 or higher.

RC 6. If a patient with RMD is offered an outpatient, day-care or other type of hospital-appointment, patients and members of the rheumatology team should follow local guidance for infection prevention and control, including the use of personal protection equipment if indicated.

If the decision is made to see the patient physically, then the patient as well as all members of the rheumatology team should do everything necessary to prevent SARS-CoV-2 infection during the visit. Since local guidance may differ, and supplies may be a limiting factor, a generic advice is given here. Personal protection equipment refers to masks, gloves, eye protection, safety footwear, gowns and hairnets, among others.

Level of agreement: 9.9±0.2; 94% scored 8/10 or higher.

Management of COVID-19 in the context of RMD

Recommendations 7-10 refer to scenarios in which a patient with RMD has been in contact with a virus-positive patient or is virus-positive him/herself. A focus is on the use of (potentially) immunosuppressive drugs, commonly used in patients with 'inflammatory' RMD.

RC 7. Patients with RMD who have been in contact with someone who has tested positive for SARSCoV-2 but is asymptomatic should be tested for SARS-CoV-2 themselves.

This recommendation raised a lot of dissent in the taskforce. The initially proposed version of this recommendation included more specific guidance about DMARD drug pausing (proposed to be done), the duration of such a drug pause (proposed for 6 days) and the recommencement of paused drugs (proposed when a virus-test is negative and symptoms of COVID-19 do not occur). Taskforce members disagreed about the need to pause, the duration of a pause and the safety of recommencement, and therefore it was decided not to include these issues in the recommendation. Although testing is recommended for patients with RMD who were in contact with a virus-positive case, taskforce members acknowledge that test-supplies may fall short or are not (yet) broadly available in many countries.

Level of agreement: 8.0±2.5; 63% scored 8/10 or higher.

RC 8. If a patient with RMD and symptoms of COVID-19 is chronically treated with glucocorticoids, this treatment should be continued.

Glucocorticoids (GC) deserve a special mention in view of the fact that GC cannot be stopped at once and should sometimes even be dose-increased in case of severe concomitant disease ('stress-scheme'). Members argued whether or not a 'lowest possible dose' should be recommended specifically, but agreed that the principle of 'lowest possible dose' as per existing EULAR-recommendations for the management of GC[21] is part of good clinical practice and valid under all circumstances.

Level of agreement: 8.8 ± 1.6 ; 79% scored 8/10 or higher.

RC 9. If patients with RMD experience mild symptoms of COVID-19, potential treatment changes in DMARDs should be discussed on a case-by-case basis.*

It is currently assumed that at least 80% of patients with COVID-19 will experience a relatively mild course.[22] This recommendation reiterates that, currently, we have no reason to believe that patients with RMD and COVID-19 have an increased risk of a more severe disease course attributable to the use of DMARDs. The risks seem reasonably low and some DMARDs are less suspected than others. The opinions in the taskforce were divided on whether or not DMARDs should be paused and, if yes, which ones.

Theoretically, some DMARDs may even be protective (eg. HCQ, IL-6 inhibitors, tumour necrosis factor inhibitors, JAKi), while for others (eg. methotrexate) pausing for a short period of time is futile due to their pharmacokinetic properties.

The taskforce finally agreed that, on balance, patient's fears and beliefs may be decisive. They finally agreed on a recommendation for a case-by-case judgement. That means: rheumatologists should not automatically advise a patient to stop DMARDs in case of mild symptoms of COVID-19 but, if the patient feels safer by pausing a DMARD for a while, and the rheumatologist believes that there is no increased risk of RMD complications, pausing the DMARD may be a defensible decision.

NSAIDs, under suspicion for a short while,[23] can as far as we know be used without additional risk and deserve no further specific mention in the recommendation.

In the risk assessment process, it should be borne in mind that many of these drugs including NSAIDs and cytokine inhibitors can potentially mask certain COVID-19 symptoms such as fever. Note also that IL-6 inhibitors and JAK-inhibitors decrease the acute phase response irrespective of the clinical course.

Level of agreement: 8.9 ± 1.4 ; 84% scored 8/10 or higher.

*RC 10. Patients with RMD and initially mild symptoms who experience worsening** of COVID-19 symptoms should immediately seek further health care advice of an expert in treating COVID-19, such as a pulmonologist, an internist or a specialist in infectious diseases, dependent on local circumstances.*

This recommendation emphasizes the potential severity of COVID-19 infection in a minority of patients (we currently assume in less than 20% of those infected) after a 5-10-day course of relatively mild symptoms. An unknown proportion of them will develop symptoms of CRS (see Box 2). Patients with worsening should not hesitate to consult an expert in the treatment of COVID-19. Rheumatologists who have been contacted by their patients and have advised them in line with recommendation 8 and 9 should be alert on potential aggravation of initially mild disease and refer patients accordingly. Level of agreement: 9.8 ± 0.5 ; 94% scored 8/10 or higher.

*RC 11. Patients with RMD who are admitted to the hospital because of significant*** COVID-19 should follow local treatment recommendations for COVID-19 as applied by the treating expert.* This recommendation elaborates on OP2 and states that, given the lack of proven effective treatments for COVID-19 and knowing that world-wide differences in hospital treatment protocols exist, it is in the best interest of patients with RMD and COVID-19 that local guidelines rather than individual (rheumatologists') beliefs are followed. Local treatment protocols for COVID-19 may among others include experimental treatment with (hydroxy)chloroquine, antibiotics, cytokine inhibitors or inhibitors of viral replication. The evidence-base of these treatments is insufficient to allow specific recommendation for patients with RMD, but their use is not yet discouraged. Evidence is accruing rapidly, and the results of a very recent trial comparing low- and high dose chloroquine, for instance, suggest that high dose chloroquine, in use in many hospitals, may increase mortality rather than decrease it.[24]

The reasoning can also be turned around: If the rheumatologist truly believes that a particular drug may be effective but formal proof is still lacking (a situation that may arise in view of DMARDs which are now investigated for the treatment of COVID-19), he should first try to "convince" the local hospital's protocol committee to adjust the existing local treatment-protocol rather than acting on his own. Preferably, the management of RMD-patients with significant COVID-19 is a multidisciplinary matter; the consensual decision of a multidisciplinary team should be credited a higher weight than the opinion of one physician. Level of agreement: 9.7 ± 0.8 ; 89% scored 8/10 or higher.

Prevention of other infections than SARS-CoV-2

Recommendations 12 and 13 remind the rheumatologist and HPR who cares for patients with RMD of other important infectious diseases to consider in these patients. There are two reasons to focus on other infectious diseases: (i) Avoiding confusion between COVID-19 and phenotypic mimics, and (ii) Avoiding severe morbidity due to neglected coexisting infections. While these recommendations

focus on three particular pathogens (pneumococci, influenza and pneumocystis Jiroveci), consideration of other infectious diseases should not be limited to these entities.

RC 12. Patients with RMD without symptoms of COVID-19 should be advised to update their vaccination status in accordance with the EULAR-recommendations for the vaccination of patients with RMD, with a particular focus on pneumococci and influenza.

This recommendation is a generic one aimed at optimizing public-health adherence. The EULAR vaccination recommendations have recently been updated using the most contemporary evidence existing for other infections than SARS-CoV-2.[25] This recommendation particularly mentions pneumococcus and influenza since they may create clinical confusion with COVID-19.

Level of agreement: 9.4±1.0; 89% scored 8/10 or higher.

RC 13. In patients with RMD treated with cyclophosphamide or glucocorticoids, pneumocystis Jiroveci pneumonia-prophylaxis should be considered.

This recommendation pertains to RMD-patients with severe lupus, severe vasculitis or systemic sclerosis, among others. It reiterates a general recommendation[26] and is mentioned here not only since PJP may be clinically confused with COVID-19 pneumonia, but also since PJP is an avoidable condition and it may be expected that the co-existence of PJP and COVID-19 pneumonia implies a worse prognosis.

Level of agreement: 9.3±0.9; 89% scored 8/10 or higher.

DISCUSSION

These 5 OP and 13 recommendations form the first EULAR set of recommendations for the management of patients with RMD during the COVID-19 pandemic. While they provide the best possible consensual guidance according to international experts, it is self-evident that their scientific status is meagre. The level of evidence never exceeds that of 'expert opinion' and the strength of recommendation is therefore axiomatically low. The taskforce expects and hopes that the lifespan of several of these recommendations will be short, far shorter than usual, as a reflection of the accrual of solid scientific evidence that may fuel better recommendations and the advent of effective drugs for COVID-19 and its complications.

Comparing these EULAR-recommendations with other recent recommendations, such as the ACR-recommendations[9] and those from Germany[2] and the UK[7], reveals, as expected, high levels of similarity, which is reassuring. Issues of controversy are sparse and of relatively minor importance.

Formulated in a more negative tone, one may say that professional organisations are currently 'flying blind', due to the novelty and the impact of the pandemic and the lack of methodologically sound evidence. Such a situation is unprecedented for all professional medical organisations including ours. Providing meaningful guidance under such circumstances asks for creative solutions that are not prescribed by Standard Operating Procedures. Many of these outstanding questions about COVID-19 in the field of RMD should be addressed in the near future. The taskforce hopes that the release of these expert-opinion-based recommendations meant for patients with RMD and their caregivers in 'COVID-time' will be a stimulus to initiate and conduct this research.

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