EULAR Recommendations for the Management and Vaccination of People with Rheumatic and Musculoskeletal Diseases in the Context of SARS-CoV-2: The November 2021 Update

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

The July 2021 update

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ABSTRACT

The first provisional recommendations on the management of rheumatic and musculoskeletal diseases (RMDs) in the context of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), largely based on expert opinion, were released more than one year ago. Afterwards, an unprecedented multitude of clinical studies have accrued in the literature and four single- or multidose SARS-CoV-2 vaccines have been approved for population-wide vaccination programs in the European Union. Studies dealing with vaccination in (inflammatory) RMDs have just released their first results or are underway.

EULAR found it opportune to look carefully to what extent these merely expert-based recommendations have stood the test of time, by challenging them against the recently accumulated body of scientific evidence, and by incorporating evidence-based advice on SARS-CoV-2 vaccination. EULAR started a formal (first) update by January 2021, performed a systematic literature review (SLR) according to EULAR's standard operating procedures, and completed a set of updated overarching principle and recommendations by July 2021, presented in this manuscript plus accompanying report with results of the SLR.

INTRODUCTION

The first set of provisional recommendations addressing 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), was released in June 2020.[1] The document addressed the implications of the pandemic for patients with rheumatic and musculoskeletal diseases (RMDs), at a time at which very little was known about the epidemiology and the clinical course of patients with RMDs who contracted SARS-CoV-2 infection, and in particular about the risks that patients with RMDs face, as well as preventive measures that these patients and their caregivers should take. The taskforce that dealt with the matter was -from a scientifical point of view- *flying blindly* and had to rely on sparse clinical experience, a lot of common sense, and only sparce scientific evidence. The taskforce therefore initially insisted on a first update within 6 months after the release of the first set. Two factors may explain the delay in updating that first set: (1) Whilst the amount of data about SARS-CoV-2 infection/COVID-19 and RMDs in the literature accrued exponentially, the content of the recommendations appeared remarkably up-to-date over time, which in the opinion of the steering committee eliminated the need for an immediate update; (2) The advent of SARS-CoV-2 vaccinations by the beginning of 2021 and the initiation of epidemiological vaccination studies in patients with RMDs made the steering group decide to issue an *ad hoc* advice on vaccination of patients with RMDs in December 2020 [2] and to postpone a formal systematic literature review (SLR) until meaningful studies had been published.

Finally, EULAR decided to start the update process in January 2021 with a formal two-tier SLR, one covering the preceding year and a deadline of March 29, 2021 and one covering the remaining three months and a deadline of May 31, 2021.

As stated previously,[1] EULAR does not intend to overrule existing guidelines at the country-level of EULAR member states. EULAR aims to provide a synthesis of the best available evidence ('the SLR') and the aggregated expert opinion, to inform rheumatologists and other health care providers (HCP), as well as patients with RMDs about management decisions to be taken in the context of the global pandemic.

Unlike the unprecedented circumstances at the beginning of the pandemic, during which the provisional recommendations had to be developed, the taskforce has now carefully followed the standard operating procedures (SOPs) [3] for updating management recommendations. As before, the taskforce was hampered by restrictions of social distancing, preventing them to meet in person, and the complete process was conducted remotely by videoconferencing.

PROCEDURES

Focus of recommendations

These recommendations pertain to the management of patients with RMDs insofar the SARS-CoV-2 epidemic and its consequent COVID-19 disease may interfere with their usual management. The recommendations do not focus on diagnosing or treating COVID-19.

Most focus is on 'inflammatory' RMDs, because it turned out that most HCP questions, and questions by patients themselves, pertained to systemic autoimmune diseases, in particular to their treatments, as well as to the risks and benefits of vaccination against SARS-CoV-2. Having said that, these recommendations do not rule out patients with other types of RMDs.

The taskforce composition

This EULAR taskforce consists of 29 members from 11 EULAR member states. Many expert members are internationally recognized rheumatologists and immunologists with years of clinical and scientific experience, who fulfil or have fulfilled official positions in the EULAR organization. EULAR's current, past and incoming presidents (AI, GRB, IBM, JS, JWB), as well as the current chair of EULAR's committee for the quality of care (RBML) and EULAR's vice-president representing people with arthritis and rheumatism (PARE) (DW) are members of the taskforce, among others. Five seats in the task force were reserved for rheumatologists from EULAR countries who could apply for this position and were subsequently selected by the convenor (RBML). Two seats were reserved for members of the emerging EULAR network (EMEUNET) who could apply for this position and were selected by the EMEUNET steering committee. The taskforce was further completed by an expert in infectious diseases (KW), one nominated representative of the ACR (JC), three SLR fellows (FPBK, AA, AN), one senior methodologist (PMM) and one junior methodologist (VN-C). The steering committee was formed by the convenor (RBML), the two methodologists (PMM, VN-C) and the three fellows (FPBK, AA, AN). All taskforce members were informed about – or had ample experience with - the development of EULAR recommendations according to EULAR's SOPs.[3]

Handling potential conflict of interest

In accordance with EULAR's SOPs, 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 daily 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 and procedures

The steering committee convened several times by videoconference and prepared the taskforce meetings and the SLR, as well as the updates for overarching principles (OPs) and recommendations, all for discussion and decision making in the entire taskforce. The steering committee, in particular the convenor and methodologists, supervised the fellows' work in the SLR, discussed the application of instruments for risk of bias assessment, performed together with the fellows the actual risk of bias assessment, and approved the reports of the SLR for releasing among the taskforce members. Finally, the steering committee solicited the levels of agreement among the taskforce members (by anonymous online survey), determined levels of evidence per item (according to the 2011 Oxford Centre for Evidence-Based Medicine), and drafted (two) manuscripts that were offered to the EULAR Council for formal approval.

The taskforce's workflow and procedures

The taskforce members took notice of the preparatory work sent to them by email and were given the opportunity to propose changes. The taskforce convened by videoconference in three separate sessions: the first on January 19, 2021, in which the research questions for SLR were established; a second meeting on May 25, 2021, in which the taskforce was informed about the results of the first tier of the SLR; and a third meeting on July 16, 2021, in which the task force was informed about the results of the second tier of the SLR and in which consensus about updated OPs and recommendations was reached. All taskforce members commented on - and agreed to - the final version of this manuscript before submission to the EULAR Council.

Target audience

In line with EULAR's SOPs, the taskforce agreed to target their guidance primarily on rheumatologists, and other HCP, and on patients with RMD and their families. Secondarily, 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, SARS-CoV-2 vaccination and availability of drugs for patients with RMD.

Systematic literature research

The procedures, course and results of the SLR are described in detail in an accompanying article.[REF]

Formal decision-making

Formal voting was only performed when deemed necessary during the final taskforce meeting on July 16, 2021. Questions for voting were formulated by the meeting chair (RL) in such a manner that a choice between two options (A and B) remained, and voting took place using the chat function of Microsoft TEAMS. Voting was not blind, results were aggregated by non-voting EULAR staff present at the meeting, and EULAR voting rules for making decisions applied (consensus accepted if >75% of the members voted in favor of the recommendation at the first round, ≥67% at the second round and at a third round >50% was accepted). If thresholds were not met, controversies were rediscussed and the voting question was reformulated for subsequent voting. This process was repeated until a formal decision was reached. Each expert's level of agreement (from 0 (no agreement at all) to 10 (full agreement)) with the statement was solicited after the final task force meeting by anonymous online survey for each OP and recommendation. 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 previous version of the recommendations contained 5 OP and 13 recommendations.[1] In the update process, the taskforce finally agreed on 5 OPs and 9 recommendations (Table 1). The bullet-text of these OP and recommendations can be read in Table 1. Below, an item-by-item discussion serves to give insight into the train of thought of the taskforce members, focuses on how previous items and new items relate to each other and provides a justification for amendments and additions.

Table 1. EULAR recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2: The July 2021 update

	Overarching principles	Mean (SD) LoA	%≥8/10
1.	In general, patients with RMD do not face more risk of contracting SARS-CoV-2 than individuals without RMD, and do not have a worse prognosis when they contract it.	8.8 (1.5)	81
2.	The diagnosis and treatment of COVID-19 in patients with RMD is the primary responsibility of an expert in treating COVID-19.	9.9 (0.3)	100
3.	Rheumatologists are the leading experts for the immunomodulatory or immunosuppressive treatments of their patients and should be involved in the decision to maintain or discontinue them.	9.9 (0.4)	100
4.	In view of their expertise, rheumatologists should be engaged in the generation of local hospital, regional or national guideline committees for COVID-19 management.	9.2 (1.2)	89
5.	The off-label use of immunomodulatory or immunosuppressive drugs for the treatment of COVID-19 outside of established guidelines, protocols or clinical trials should be discouraged.	9.2 (1.2)	93
	Recommendations		
1.	Patients with RMD should be strongly advised to comply with all infection prevention and control measures prescribed by public health authorities, before and after SARS-CoV-2 vaccination.	9.9 (0.2)	100
2.	Patients with RMD should be advised to receive a SARS-CoV-2 vaccination with any of the single or multidose EMA-approved vaccines.	9.6 (1.6)	96
3.	Patients with RMD who have been vaccinated against SARS-CoV-2 should be advised to continue their treatment unchanged; those who have not been vaccinated should be advised to continue their treatment, taking into account that certain therapies have been associated with an increased risk of severe COVID-19.	9.5 (0.6)	100
4.	If a patient with RMD receiving long-term glucocorticoid treatment develops suspected or confirmed COVID-19, this treatment should be continued.	9.3 (0.9)	96
5.	If a patient with RMD receiving rituximab treatment contracts SARS-CoV-2, postponing the next cycle of RTX should be considered.	9.7 (0.6)	100
6.	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.	9.9 (0.3)	100
7.	Patients with RMD should be advised to update their general vaccination status in accordance with the EULAR recommendations for the vaccination of patients with RMD, with a particular focus on pneumococci and Influenza.	9.7 (0.6)	100
8.	In patients with RMD not using immunomodulatory or immunosuppressive treatment, SARS-CoV-2 vaccination should precede a treatment start with such therapy if clinically feasible.	9.6 (1.1)	93
9.	In patients with RMD using rituximab or another B-cell depleting therapy, SARS-CoV-2 vaccination should be scheduled in a way to optimise vaccine immunogenicity.	9.6 (1.1)	96

LoA: Level of Agreement (between 1 and 10), Mean(SD): Mean level of agreement (standard deviation), RMD: Rheumatic Musculoskeletal Disease, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, COVID-19: Coronavirus Disease 2019, EMA: European Medicines Agency, RTX: Rituximab.

Old 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.

New OP 1. In general, patients with RMD do not face more risk of contracting SARS-CoV-2 than individuals without RMD, and do not have a worse prognosis when they contract it.

New OP 1 is almost unchanged, but its evidence base has importantly improved, as the results of the SLR demonstrate. While the old OP1 was preceded by the words *To date,* in order to reflect the scarcity of reliable data, many studies have been published thereafter and testify to the truth of the statement. This statement pertains to the incidence of COVID-19 among patients with RMD, as well as to the risk factors for contracting COVID-19 and for an unfavourable clinical course of COVID-19: incidence, risk and course are globally the same as in the general population.

The words *In general* have been added to the **new OP 1** to refer to a few situations in which the accuracy of the global statement can be disputed. Examples are patients with some rare and severe systemic autoimmune diseases and some autoinflammatory diseases. [REF] Obviously, as a consequence of their scarcity, these exceptional cases have not yet been studied well. The same reservation pertains to certain treatments that have been associated with a worse course, such as glucocorticoids (discussed under **new RC 4**), mycophenolic acid (or mycophenolate mofetil)(MMF), rituximab (RTX) and potentially Janus kinase inhibitors (JAKi) (discussed under **new RC 3**). The taskforce argued that either methodological considerations preclude a firm(er) stand, or that the drug in question was too infrequently investigated in studies to base a general statement on. While these examples are more explicitly addressed in the SLR for reference, [REF] they were kept out of the realm of the OP and recommendations (the exception to the rule is rituximab, as further outlined below).

Level of agreement: 8.8/10

Deleted: a

Old 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.

New OP 2. The diagnosis and treatment of COVID-19 in patients with RMD is the primary responsibility of an expert in treating COVID-19.

This OP did not change importantly. It was considered more obvious now than it was in the past that other medical experts than rheumatologists are primarily responsible for the treatment of COVID-19. The taskforce felt that further specification of those experts was redundant and beyond the scope of this taskforce, especially since the situation may vary per country, per region, and per hospital.

Level of agreement: 9.9/10

Old 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.

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

While this OP has not substantially changed, the term 'immunomodulatory or immunosuppressive treatment' is introduced here for the first time, and will be used throughout the entire document. Already from the beginning (in April 2020) there was dissent about using the term 'immunosuppressive' vs. 'immunomodulatory', which led to an explanatory Viewpoint by *Isaacs and Burmester*,[4] who argued that some of the drugs used in rheumatology are 'immunomodulatory' (e.g. targeted therapies), while others are 'immunosuppressive' (e.g. glucocorticoids, azathioprine and MMF), and that the 'immunosuppressive designation should not be used to cover all these drugs. Therefore, the task force decided to use the terminology 'immunomodulatory or immunosuppressive' throughout the document.
Level of agreement: 9.9/10

Old 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.

New OP 4. In view of their expertise, rheumatologists should be engaged in the generation of local-hospital, regional or national guideline committees for COVID-19 management.

This OP has been condensed by virtue of evolving evidence. During the pandemic, it has become clear that some of the treatments often used by rheumatologists have gained a prominent position in the management of patients with a hyperinflammatory state due to COVID-19, since randomised controlled trials (RCT) have proven their efficacy, [REF] while a drug like hydroxychloroquine, promoted as a potentially life-saving compound in the beginning of the pandemic, has clearly been discredited after the results of several RCTs had been released. [REF] What remains is that rheumatologists are the experts who have most experience in the benefits and harms, pharmacokinetics and pharmacodynamics of glucocorticoids and targeted therapies, such as

interleukin-6-receptor (IL-6R) inhibitors and JAKi, and it appears common sense to involve rheumatologists in guideline developments that include such treatments for COVID-19.
Level of agreement: 9.2/10

Old 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.

New OP 5. The off-label or off-guidelines use of immunomodulatory or immunosuppressive drugs for the treatment of COVID-19 outside of established guidelines, protocols or clinical trials should be discouraged.

Commented [MX1]: I think we agreed at the 16-July meeting for adding this word

Proposal: in view of recent delivery problems of tocilizumab: keep the old OP5
I do not agree. I think we should use the new one and add "or off-guidelines". I just remain that WHO has provided on July 6 a "strong recommendation for using anti-IL-6 receptor Ab in severe and critical COVID" and we cannot argue against that on the fact that our patients may have some problems for getting the drug. We have alternatives for our patients and TCZ is going to decrease by 20% the rate of death in severe COVID patients

The initial fear for a shortage of scDMARDs for RMD-patients (with or without COVID-19), due to overuse for the treatment of COVID-19 patients, which formed an important element of the previous OP 5, has not been materialized. As said, hydroxychloroquine is ineffective in COVID-19, and will not be used for that indication anymore. Glucocorticoids (including dexamethasone), now part of most COVID-19 treatment protocols worldwide, are widely available and shortages are not expected. After a long period of ambivalence, invoked by RCT with varying results, finally the IL-6R-inhibitor tocilizumab has been proclaimed an effective treatment for COVID-19, in particular for those with severe COVID-19 and largely restricted to the (short) hyperinflammatory phase. While tocilizumab has not been labelled for the indication of severe COVID-19, the drug has been included in treatment protocols worldwide, [REF] and anti-IL-6 receptor antibodies have been strongly recommended by WHO live guidelines in this situation (ref) which has led to an increased demand for tocilizumab. Still, this increase seems to be trivial in light of the fact that patients with severe COVID-19 need only one or two intravenous doses and the manufacturer of tocilizumab has had ample time to adapt its production facilities. Therefore, the manufacturer's announcement of temporary delivery problems of tocilizumab, and its internal prioritisation of rare non-rheumatological indications (eg. tocilizumab for the prevention of cytokine storm syndrome after CAR-T-cell therapy) versus rheumatological

Commented [MX2]: BMJ 2020;370:m3379 http://dx.doi.org/10.1136/bmj.m3379

indications, has struck the professional rheumatological community with disbelief. The situation has led to the release of guiding principles by several professional organisations aiming at replacing tocilizumab by compounds with similar mechanism of action, or at choosing a different administration route. [REF]

In view of recent delivery developments, this taskforce decided to maintain its warning against the off-label or off-recommendation use of immunomodulatory or immunosuppressive treatment.

Level of agreement: 9.2/10

Deleted: to not suspend the warning about shortage of DMARDs, and

General measures and prevention of SARS-CoV-2 infection

The old recommendations 1-3 included general public health measures and precautions, meant for RMD patients without symptoms of SARS-CoV-2 infection, who had not been in contact with SARS-CoV-2 infected patients. By the end of 2020, SARS-CoV-2 vaccination became available and nowadays arguably forms the key measure of prevention of COVID-19 for RMD-patients and beyond.

Old 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.

New RC 1. Patients with RMD should be strongly advised to comply with all infection prevention- and control-measures prescribed by public health authorities, before and after SARS-CoV-2 vaccination.

This recommendation remains largely unchanged, but wording is added to reiterate that preventive measures remain important after (full) vaccination, in order to prevent asymptomatic but infected RMD patients from unknowingly spreading the virus, even though they may themselves be well protected against severe COVID-19 (hospitalisation). Ongoing studies will hopefully reveal to what extent spreading of virus by asymptomatic individuals, as well as mild COVID-19 itself, is prevented by full SARS-CoV-2 vaccination.

Level of agreement: 9.9/10

Old RC 2. *Patients with RMD should in general be advised to comply with the same preventive and control measures as patients without RMD.*

The taskforce felt that, in analogy with **new OP 1**, and by virtue of evolving evidence supportive of new OP 1, this recommendation has become redundant.

New RC 2. Patients with RMD should be strongly advised to receive a SARS-CoV-2 vaccination with any of the single- or multidose EMA-approved vaccines.

In line with previous EULAR recommendations, issued in December 2020, [6] as well as with evolving evidence outlined in the SLR,[REF] the taskforce strongly felt that patients with RMD should be motivated and convinced to receive full SARS-CoV-2 vaccination with one of the approved vaccines. On the basis of the available evidence, the taskforce was of the opinion that there are no compelling arguments to prioritize or dismiss particular approved vaccines for reasons of less efficacy or increased adverse events, following European Medicines Agency (EMA)-guidance.[7] However, the taskforce stipulates that patients and HCP must follow national guidelines that are in place, which may sometimes deviate from EULAR's general principle of equal advisability.

The taskforce discussed the desirability of other SARS-CoV-2 vaccines than those approved by the EMA, an issue that is opportune in some EULAR-affiliated countries, but decided that only EMA-approved vaccines should be positively recommended in EULAR guidance documents. This position does not imply that EULAR *a priori* considers non-EMA-approved vaccines as ineffective or unsafe; EULAR's stand should rather be seen as an incentive to subject not-yet-EMA-approved vaccines to EMA procedures, in order to obtain a trustworthy EMA-opinion on their efficacy and safety, which will ultimately improve vaccination rates among populations of RMD-patients and beyond.

The taskforce also discussed the advisability of an additional vaccination (after a regular vaccination series), a policy that, at the moment of drafting this document, is in the process of implementation in several EULAR-affiliated countries within- and outside Europe. The taskforce was of the opinion that - to date- there is no compelling epidemiological evidence from RCTs, or from reliable observational studies, to positively recommend about an additional vaccination, despite information that points to impaired humoral immunity (anti-SARS-CoV-2 antibody response) in some patients with autoimmune diseases who are treated with certain immunomodulatory or immunosuppressive drugs [REF OCTAVE?]. The taskforce also finds it too early to recommend that individual patients should routinely be tested for anti-SARS-CoV-2 antibodies (a policy that is not uncommon in some countries), since the documentation of these antibodies *per se* does not provide the evidence for their virus-neutralizing capacity. The taskforce is aware that studies testing the advisability of an additional vaccine-dose, after an initial primary vaccine series, with or without an antibody test, are underway and results of these studies may change the taskforce's reserved opinion in the near future.

Taken together, the taskforce was of the opinion that - in the realm of suboptimal SARS-CoV-2 vaccination status, due to scarcity of vaccines, fear of vaccination or inappropriate vaccination information – it is more important to improve vaccination status among the still unvaccinated RMD-

Commented [MX3]: Not true anymore;
-We have the demonstration in the general population from Israel that a 3rd dose 6 months after the second one is clinically efficient after 6 months in the general population over 60.
-In numbers of countries it is officially recommended by the authorities to provide a 3rd dose to all patients on RTX, MMF cyclophosphamide, on steroids more than 10 or 20 mg/day

patients than to administer an additional vaccine-dose to those that have already been fully vaccinated and can be assumed to have a basic level of protection against SARS-CoV-2. In line with this position, and in light of the worldwide reach of EULAR recommendations, the taskforce encourages rheumatology societies of EULAR-affiliated countries to motivate their governments to facilitate the distribution of vaccines from high-income countries to medium- and low-income countries, so that RMD-patients worldwide can better be protected.
Level of agreement: 9.6 /10

Commented [MX4]: Again not completely agree. Today the 2 tasks are equally important if we consider for the 3rd dose in aged patients 6 months after the 2nd dose and in patients treated with drugs listed above
For countries having arrived to vaccine a great majority of the population, the challenge is now to maintain this immunity

Old 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.

New RC 3: Patients with RMD who have been vaccinated against SARS-CoV-2 should be advised to continue their treatment unchanged; those who have not been vaccinated should be advised to continue their treatment, taking into account that certain therapies have been associated with an increased risk of severe COVID-19.

The old set of recommendations made a distinction between patients with RMD (and treatment) at risk of COVID-19 and those who had (already) contracted COVID-19. The somewhat premature advice (old RC 3) to continue drug-treatment in symptomless RMD-patients at risk of COVID-19 has proven validity by evolving evidence, but has also gained dimension by the advent of SARS-CoV-2 vaccines. The **new RC 3** makes a distinction between those who have been vaccinated against SARS-CoV-2, and those who have not (yet).
The vaccinated patients may, in the opinion of the taskforce members and based on evolving evidence, safely continue their immunomodulatory or immunosuppressive treatment unchanged, even though an optimal humoral immune response may not occur under treatment. The taskforce was of the opinion that *any protection* is better than *no protection* and that temporarily discontinuing treatment of RMD bears the risk of flare, and also points to the fact that an optimal immune response against SARS-CoV-2 is not unambiguously defined.
The not (yet) vaccinated patients should realize that the likelihood of severe COVID-19 is increased with certain immunomodulatory or immunosuppressive treatments, as outlined in the SLR,[REF] in particular in patients with certain (rare) autoinflammatory syndromes and in those who are treated with RTX and perhaps JAKi. This recommendation should be read as an encouragement to patients and HCP to optimize vaccination status for SARS-CoV-2, taking certain precautions into account (as further outlined below).
Level of agreement: 9.5/10

Management of the RMD when local measures of social distancing are in effect

Old 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.

Old 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.

Old 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.

The old recommendations 4-6 advised patients with RMD how to act when official restrictions in the freedom of movement apply. They referred to social distancing, varying from keeping 1, 1.5 or 2-meter distance for subpopulations to a complete country-lockdown. When discussing the advisability of these three recommendations, the taskforce agreed that their content was overtaken by reality and evolving evidence. This does not mean that the recommendations were wrong, or have become obsolete, but rather that the professional rheumatological community and RMD-patients have become entirely accustomed to remote monitoring (old RC 4), initiating DMARD-treatment during the pandemic (old RC 5) and triaging those who need a face-to-face consultation (old RC 6). Therefore, the taskforce decided to erase these three old recommendations and further refer for this matter to EULAR guidance about remote monitoring in development. [REF]

Management of COVID-19 in the context of RMD

Old recommendations 7-10 referred to scenarios in which a patient with RMD had been in contact with a SARS-CoV-2 infected patient or had become infected him/herself, with a focus on the use of immunomodulatory or immunosuppressive drugs.

Old RC 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 themselves.

While in April 2020 this recommendation still raised dissent among taskforce members, due to the scarcity of SARS-CoV-2 tests and unclarity about the potential consequences of a positive test result (e.g., drug pause or not), this was not a source of discussion anymore in July 2021. SARS-CoV-2

testing has become ubiquitous and part and parcel of usual clinical care. The old RC 7 was considered redundant by the taskforce and therefore was dismissed.

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

New RC 4. If a patient with RMD receiving long-term glucocorticoid treatment develops suspected or confirmed COVID-19, this treatment should be continued.

In spite of several studies pointing to an unwarranted association between glucocorticoid-use and (the risk on- and course of-) COVID-19, extensively outlined in the SLR, old RC 8 (renumbered as **new RC 4**) has stood the test of time. It has even been stretched by extending its reach to RMD-patients who actually have symptoms of COVID-19. After studying the results of the SLR, the taskforce came to the conclusion that the observed increased risk of severe COVID-19 when using glucocorticoids, as well as the worse course of COVID-19 in RMD- patients with proven COVID-19, could well be explained by *confounding-by-indication*. The suggestion of a glucocorticoid dose-response that was seen in a few studies may reinforce this conclusion. While an adverse effect of glucocorticoids themselves cannot entirely be excluded, there is also sparse indirect evidence in the literature that pausing or discontinuing glucocorticoids for reasons of safety is associated with disease flaring, which in itself may contribute to an adverse outcome of COVID-19. Finally, it should also be noted that patients on long-term glucocorticoid therapy are at risk of glucocorticoid-induced adrenal suppression and may therefore require glucocorticoid supplementation in the context of major trauma, surgery or significant intercurrent infection, including COVID-19.

The advice to continue glucocorticoids in RMD-patients *without* symptoms of COVID-19 is now covered by the generic **new RC 3**; the advice to continue glucocorticoids in RMD-patients *with* suspected or proven COVID-19 is covered by **new RC 4**. The taskforce remains of the opinion that the principle of 'lowest possible dose' as per existing EULAR-recommendations for the management of medium- to high-dose glucocorticoids therapy [REF] is part of good clinical practice and valid under all circumstances.

Level of agreement: 9.3/10

Proposal of a new recommendation about treatment of our RMD patients with therapeutic aanti-Sars-CoV-2 Ab

There is a new recommendation from WHO: "Among patients with non-severe covid-19, we suggest treatment with casirivimab-imdevimab, conditional to those at highest risk of hospitalisation."

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It implies hat for our RMD patients treated with RTX, MMF, CPX, PDN more than 10, not vaccinated, or seronegative after vaccination, this treatment has to be considered if they are "contact" or have a positive PCR.

New RC 5. If a patient with RMD receiving RTX treatment contracts SARS-CoV-2, postponing the next cycle of RTX should be considered.

This new recommendation without precedent in the first set was included because of evolving evidence that patients who use B-cell depleting therapy (in particular anti-CD20 therapy with rituximab) for their RMD have a higher risk of a severe COVID-19 course and a worse antibody response to SARS-CoV-2 vaccination. [REF] The taskforce realized that there are many practical questions around the best possible management of RMD patients treated with B-cell-depleting therapy. Other professional organisations than EULAR have sometimes more pertinently recommended about B-cell-depleting therapy in association with COVID-19. [REF] REF] This taskforce was of the opinion that an evidence-based recommendation on how to act in specific circumstances is not opportune, since the data proving that specific measures are indeed effective and safe are currently lacking. Still, the taskforce felt some pressure of sister organisations to recommend on rituximab, administered in cycles with intervals ranging from 1 to 12 months. This recommendation, as well as the ones pertaining to vaccination that follow below, is based on common sense in association with clinical feasibility, rather than on solid evidence. The taskforce found it reasonable to postpone a next cycle of rituximab (or, alternatively, to replace rituximab by an equally effective drug) in a patient with stable RMD disease as long as the clinical situation allows such a postponement. That means: the risk of a treatment (rituximab) postponement in a patient with high disease activity or potentially life-threatening disease should be weighed against the (modest) additional risk of a worse COVID-19 course if rituximab is continued unchanged. While the taskforce recognizes some excess risk of rituximab in such circumstances, the contraindication for rituximab is relative, not absolute.
Unlike other professional organisations, this taskforce did not find compelling arguments to couple a time-indication (e.g., at least 4 weeks delay) to this recommendation.

Old 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.

This old recommendation reflected a compromise between taskforce members who considered the continuation of DMARDs in an RMD-patient with symptoms of COVID-19 undesirable, and those who

granted prevalence to the argument that more than 90% of COVID-19 patients usually fare a mild and self-limiting course, and that early data did not point to a significantly increased risk of severe COVID-19 in RMD patients on DMARD treatment. Since then, the ever-increasing body of evidence has tipped the balance towards a more moderate and lenient attitude of continuing DMARDs in case of mild COVID-19 symptoms. Herewith, this old RC 9 has become redundant, and its content is now entirely covered by **new RC 3**.

Old 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.

New RC 6: Patients with RMD and initially mild symptoms who experience worsening of COVID-19 symptoms should immediately seek further health care advice from an expert in treating COVID-19.

While consensus has now been obtained regarding the continuation of DMARDs in a patient with mild COVID-19, it is still opportune to advice on RMD patients with worsening of COVID-19. They should be referred to an expert in COVID-19, not being the rheumatologist, as per **new RC 6**.
It has become clear during the pandemic that approximately 10% of patients with COVID-19 will experience a more severe course. Severe COVID-19 patients, with or without RMDs, may require ventilatory support, antibiotic treatment, anticoagulation treatment and temporary immunomodulatory or immunosuppressive treatment. While some of these treatments involve medication with which rheumatologists are considered broadly familiar, the taskforce is (still) of the opinion that the diagnosis of severe COVID-19, the indication to start adjunctive therapy and the monitoring of the course of severe COVID-19 belong to the realm of an expert in COVID-19 (**new OP 2**). This does not mean that rheumatologists should not be involved in the design of- and discussion about- protocols and guidelines, as per **new OP 4**. For more details about the immunomodulatory treatment of (severe) COVID-19 *per se*, the taskforce refers to the EULAR's points to consider on the use of immunomodulatory therapies for COVID-19. [REF]
Level of agreement: 9.9/10

*Old 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 dates back to the time at which taskforce members made a deliberate distinction between patients with mild COVID-19, those with worsening of once mild COVID-19, and those with significant or severe COVID-19. This distinction has gradually become outdated and

redundant for the advice of how to manage RMD patients with symptoms of COVID-19 today. Those with mild symptoms may continue their treatment unchanged and followed up until recovery, as per **new RC 3**. Those with worsening symptoms (see Box-text) should be referred to an expert in COVID-19 without exception, as outlined in **new RC 6.** Herewith, old RC 11 has become redundant.

Prevention of other infections than SARS-CoV-2

Old recommendations 12 and 13 intended to remind the rheumatologist of potentially coexisting comorbid infections for which regular vaccinations exist (old RC 12), and of other important infectious diseases that could phenotypically mimic COVID-19 (old RC 13).

Old 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.

New RC 7: Patients with RMD should be advised to update their general 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 was essentially unchanged, though the current presence of COVID-19 symptoms was regarded irrelevant. [REF]

Level of agreement: 9.7/10

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

This recommendation pertaining only to a small minority of patients with RMD, particularly those with intense immunosuppressive therapy, served to increase the rheumatologist's attention to a phenotypical mimic of COVID-19 at a time at which confirmatory COVID-19 testing was not self-evident. The taskforce was of the opinion that clinical confusion between *pneumocystis Jiroveci pneumonia* (PJP) and COVID-19-pneumonia has become unlikely to date. While PJP-prophylaxis remains highly topical for those at risk of PJP due to (severe) immunosuppression, the taskforce was of the opinion that this is out of the scope of the current manuscript and the old RC13 could be deleted.

New recommendations

The taskforce added two recommendations referring to SARS-CoV-2 vaccination that had no precedent in the old set of recommendations.

New RC 8: In patients with RMD not using immunomodulatory or immunosuppressive treatment, SARS-CoV-2 vaccination should precede a treatment start with such therapy if clinically feasible.

This recommendation finds its justification in recent evidence, summarized in the SLR,[REF] pointing to an impaired humoral immune response in RMD patients treated with particular immunomodulatory or immunosuppressive treatments. The level of impairment varies by compound: from the occasionally profound suppression of humoral immune response in case of B-cell-depleting therapy and mycophenolate, to the generally mild to moderate impairment in case of methotrexate, glucocorticoids and JAKi, to no distinguishable impairment for TNF-inhibitors and IL-17-inhibitors, as well as for most conventional synthetic DMARDs. While the taskforce agreed that the clinical significance of an impaired level of antibodies to SARS-CoV-2 (humoral immune response) is still unclear (it does not necessarily mean that the entire defence against SARS-CoV-2 is compromised, namely cell-mediated immunity), it also argued that prevention of a potentially hazardous scenario is preferable, as long as the actual clinical situation for which the immunomodulatory or immunosuppressive treatment is indicated does not stand in the way. That means: First vaccinate, then start with immunomodulatory or immunosuppressive therapy, unless the delay of treatment is damaging or life threatening, a consideration that is left at the discretion of the rheumatologist and the patient in shared decision.
Level of agreement: 9.6/10

New RC9: In patients with RMD using rituximab or another B-cell depleting therapy, SARS-CoV-2 vaccination should be scheduled in a way to optimise vaccine immunogenicity.

This new recommendation serves to bring the EULAR recommendations in sync with guideline documents of professional sister organisations that have recommended explicitly on this matter.[REF] It asks the rheumatologist's, HCPs, and patient's attention for the fact that -as outlined above several times- B-cell depleting therapy may compromise the development of an appropriate (humoral) defence against SARS-CoV-2 upon vaccination. While **New RC 8** points to postponement of the start of immunomodulatory or immunosuppressive treatment when clinically feasible, it does not suffice for patients who have already been treated with cycles of rituximab, which may surely cause a long-lasting and not immediately reversible functional suppression of B-cell activity. The taskforce acknowledged that patients and HCP ask for more specific guidance in terms of a minimal duration

between the last cycle of rituximab and the vaccination, but had to conclude that such a time indication does not logically follow from the currently available data; the highly variable B-cell repopulation kinetics may in fact be a more important factor to take into account when deciding when to vaccinate rather than a specific timeframe. The task force realizes that the advice to *optimize vaccine immunogenicity* [sic] without further explication may not fully cover patients' and HCP's expectations. However, in the absence of evidence, albeit in spite of existing guidance from other organisations, the taskforce feels they could not be more specific at this point in time.
Level of agreement: 9.6/10

DISCUSSION

This set of 5 OPs and 9 recommendations forms the first update of the original EULAR provisional recommendations for the management of patients with RMD during the SARS-CoV-2 pandemic. The scientific status of the first set was meagre, but the level of evidence of the updated recommendations has significantly improved, in sync with evolving knowledge. However, there is still a lot to gain. Despite an exponential and likely unprecedented explosion of scientific studies, many critical clinical questions, some of which are mentioned in the research agenda (Table 2), have not yet been addressed adequately in clinical studies and remain largely unanswered. Whilst the overall impression is not a negative one, the majority of available studies still received the predicate of *unclear* or *high* risk of bias. Those few studies with *low* risk of bias, the best ones so to say, have had a significant impact on the reformulation of the old recommendations into new ones.

Old vs. new recommendations

When comparing the old and new recommendations, a few observations stand out.

The first is that the number of recommendations has reduced from 13 to 9 and the length of each recommendation has importantly reduced too. This may seem a trivial observation without scientific meaning, but may also testify of an increased maturity of the field and (consequently) more unanimity among taskforce members. That levels of agreement were (even) higher than in the previous set, adds to the credibility of the latter. In April 2020, diverging opinions, due to lack of available evidence and a necessary reliance on (sparse) experience (not to say: beliefs), had materialized into a rather high number of rather verbose recommendations, in order to better reflect different, sometimes even opposing opinions. In July 2021, after properly being informed by the SLR-committee, the taskforce reached consensus within 3 hours of discussion, and delivered 9 concise and structured recommendations.

The second observation is that the content of the updated set is dominated by SARS-CoV-2 vaccination. SARS-CoV-2 vaccination is indisputably an example of unprecedented medical progress. While in April 2020 the prospect of SARS-CoV-2 vaccination was still uncertain, in July 2021, at the conception of this manuscript, half of the population in EULAR countries were already vaccinated and discussions about (and implementation of) an additional vaccine dose have started, albeit confirmatory evidence for that policy is still lacking.

More focus on vaccination also illustrates the progress that has been made in understanding the hazards that RMD patients face in the context of COVID-19. Many had feared that patients with RMD were not only at higher risk of contracting COVID-19, but would also fare a worse course once they had contracted COVID-19. In spite of a couple of exceptions and uncertainties, amply described in

the accompanying SLR,[REF] this fear has not become fact and the updated set of recommendations is a good reflection of that appreciation; RMD patients are not very different from unaffected individuals in the population, most treatments can be safely continued, and special precautions for RMD-patients are in general not necessary.

This does not mean that there are no outstanding questions anymore. JAKi have recently been associated with an increased risk of severe COVID-19, rituximab is a notoriously difficult therapy to manage in the context of COVID-19 and vaccination, and there are also question marks about some truly immunosuppressive drugs such as mycophenolate, a group of drug prescribed for several systemic autoimmune diseases, about which the first impressions were slightly worrisome. Still, the make-up of the studies that released these associations preclude a causal interpretation; selection bias and confounding-by-indication, rather than the drug itself, may be responsible for the reported excess risk in many studies.

New EULAR recommendations into context

Comparing these EULAR recommendations with other recent recommendations, such as the latest version of the American College of Rheumatology (ACR) recommendations, [9] reveals, as expected, high levels of similarity. Issues of controversy are of relatively minor importance. The ACR has released guidance documents that have been more frequently updated than EULAR's, and are far more detailed, since they deal with several scenarios and drugs separately. [REF] A main discrepancy pertains to ACR's recommendation of a drug-pause for most DMARDs in case of known or suspected SARS-CoV-2 exposure. ACR also advices to pause DMARDs in case of active or presumptive COVID-19 (exceptions are sulfasalazine and conditionally IL-6 inhibitors). Reinitiating treatment should, according to the ACR, depend on COVID-19 symptom resolution (after at least 7-14 days, or more for certain DMARDs). The British Society of Rheumatology (BSR)[REF] and the UK's National Institute of Clinical Excellence (NICE)[REF] also advice to pause DMARDs for a while in case of manifest COVID-19. The EULAR taskforce is definitely more lenient in this regard, since it does neither recommend to pause in case of exposure to SARS-CoV-2, nor in case of mild symptomatic COVID-19 (i.e., those ≈90% of COVID-19 patients that do *not* require oxygen-supplementation or hospitalization). In case of more severe (hospitalized) COVID-19, EULAR leaves the decision about pausing or stopping DMARDs at the discretion of the treating physician for COVID-19 (**new OP 2**), in consultation with the treating rheumatologist (**new OP 3**). Whether this discrepancy in policies results from a different interpretation of the available literature, from different local circumstances or from differences in medicolegal context between Europe and the US, is unclear.

Regarding SARS-CoV-2 vaccination, EULAR has aggregated management recommendations and vaccination recommendations into one document. The ACR has recently released a guidance

document entirely dedicated to SARS-CoV-2 vaccination in patients with RMDs.[REF] The ACR has provided no less than 76 guidance statements to cover all possible scenarios that patients with RMD may encounter. Basically, these ACR-statements are in line with EULAR's simple and concise recommendation that all patients with RMD, without exception, should be fully vaccinated as soon as possible (**new RC 2**). The ACR provides more detailed guidance on how to manage RMD patients in specific scenarios (the ACR, for instance, advices to pause certain DMARDs around vaccination, gives specific advice per DMARD, and provides timelines). The EULAR taskforce was aware of the ACR document, and discussed these matters, but was essentially of the opinion that the available scientific evidence precluded such a detailed level of advice. The taskforce decided that a more generic advice was opportune (**new RC 2**), which could rely on a very high level of agreement among taskforce members. It is to be expected that the ACR guidelines in subsequent versions will become more generic and less detailed, once robust evidence evolves.

A critical appraisal of evolving epidemiological evidence on SARS-CoV-2/COVID-19

Translating scientific evidence, stemming from high-profile epidemiological surveys, RCTs or high-quality observational studies, to the situation of the individual patient in daily clinical practice is not an easy task. Communicating such information properly to patients is even more difficult. Big-data studies and multi-country epidemiological registries will often attract most attention from physicians and lay press, because of the high numbers of patients involved in such studies. Not infrequently do these studies report small but statistically significant excess risks for RMD patients in comparison to the general population. It is of utmost importance for HCP, who have to deal with individual patients rather than an entire population of patients, to realize that a small excess risk (risk estimates arbitrarily between 1 and 2-3) is often irrelevant if the base case risk for that patient is low, even if the small excess risk is highly statistically significant. The anticipated consequence (e.g., lower risk of severe COVID-19) of a certain interventional recommendation (e.g., DMARD pausing), seemingly justified by an excess risk at the group level, should always be weighed against unwarranted and often unforeseen consequences of that interventional recommendation (e.g., relapse of disease activity). In addition, the taskforce realized that the technical demonstration of an association between an exposure (e.g., the use of a DMARD) and an outcome (e.g., hospitalisation for COVID-19) does not suffice to recommend an intervention (e.g., pausing the DMARD) if the proof that such an intervention really works is lacking.

The taskforce investigated in the SLR many studies with small excess risks, determined in large groups of patients, sometimes statistically proven. Most of these studies were considered of too low methodological quality to give them much credit. But on top of that, the taskforce judged many of those small excess risks as having too little impact on individual patients with RMDs anyway, to

justify an interventional recommendation that deviates from the norm (e.g., DMARD-pausing instead of continuing DMARDs unchanged).

Conclusion

The taskforce hopes that these updated, now more evidence-based, recommendations on how to manage patients with RMDs in the context of SARS-CoV-2 and COVID-19 give HCPs the tools to make clinical decisions about SARS-CoV-2 prevention, DMARD management and SARS-CoV-2 vaccination. More importantly, it hopes that it will help building trust among patients with RMDs, that their risk of severe COVID-19 is not importantly increased and that SARS-CoV-2 vaccination, the only means to finally contain the pandemic, can safely take place.

RESEARCH AGENDA (to be further developed)

General measures and prevention of SARS-CoV-2 infection

1. Large unselected registry studies to assess the course of COVID-19 in patients with rare autoimmune diseases compared to the general population.

2. …

3. …

DMARD management of RMD patients with COVID-19

1. Large unselected registry studies to assess the risk of JAKi and immunosuppressants (glucocorticoids, azathioprine, cyclosporine, cyclophosphamide, mycophenolate and tacrolimus) on a worse course of COVID-19.

2. Studies to assess the impact of other B-cell depleting strategies (e.g. belimumab) on the outcome of SARS-CoV-2 infection

3. Studies to compare different DMARDs management strategies in the context of SARS-CoV-2 infection: unchanged, versus dose reduction versus interruption in patients with RMDs.

Vaccination of the RMD patient

1. Large observational studies to assess the risk and course of post-vaccination COVID-19 in patients with inflammatory RMDs using immunomodulatory or immunosuppressive medication.

2. Studies to assess the impact of temporarily stopping medications “of concern” before or after SARS-CoV-2 vaccination, in order to improve immunogenicity (and the impact of such strategies on disease activity and need of additional treatments e.g. steroids)

3. Studies to assess the impact of an additional dose after an initial primary SARS-CoV-2 vaccine in selected subsets of patients with RMD, in order to improve the humoral and/or cell-mediated immunity to SARS-CoV-2 vaccines.

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DISCLOSURE OF COMPETING INTERESTS

The following authors have disclosed potential conflicts of interest:

RL received honoraria for lecturing and consultation from AbbVie, Amgen, BMS, Celgene, Galapagos, Gilead, Janssen, Eli Lilly, Novartis, Pfizer, UCB and is owner and director of Rheumatology Consultancy BV.
FK has nothing to declare.
AA has nothing to declare
AN
JB
GB received honoraria for lectures and consulting from AbbVie, Amgen, BMS, Gilead, Janssen, Lilly, Novartis, Pfizer, Sanofi-Aventis, Roche, UCB.
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RC
JC
OE
MH
LH
AI
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IAJ
SM
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