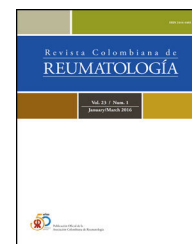




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Reflexion Article

Recommendations for rheumatologists on pharmacological management during the COVID-19 health emergency: Expert group opinion[☆]



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ABSTRACT

Coronavirus 2019 (COVID-19) is an unexpected pandemic that has caused a state of emergency, as well as generating drastic changes in clinical care protocols. Some drugs commonly used in rheumatoid arthritis, systemic lupus erythematosus, and other systemic autoimmune diseases have been described for its treatment. Therefore, there is an imminent risk of shortages. The aim of this narrative review and expert opinion is to present general recommendations on the clinical and administrative management of outpatients with autoimmune or systemic inflammatory disease, in the context of the COVID-19 pandemic.

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Recomendaciones para reumatólogos sobre el manejo farmacológico durante la emergencia sanitaria por COVID-19: opinión de un grupo de expertos

R E S U M E N

Palabras clave:

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La enfermedad por Coronavirus 2019 (COVID-19) es una pandemia inesperada que ha provocado un estado de emergencia y que ha generado cambios drásticos en los protocolos de atención clínica. Para su tratamiento se ha descrito el papel de algunos medicamentos usados habitualmente en artritis reumatoide, lupus eritematoso sistémico y otras enfermedades autoinmunitarias sistémicas. Debido a ello, existe un inminente riesgo de desabastecimiento, por lo cual el objetivo de esta revisión narrativa y opinión de expertos es formular recomendaciones generales clínicas y administrativas sobre el manejo de pacientes ambulatorios con enfermedad autoinmunitaria o inflamatoria sistémica en el contexto de la pandemia por COVID-19.

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Introduction

Betacoronavirus SARS-CoV-2 infection, which causes the coronavirus 2019 (COVID-19), disease, is an unexpected pandemic that has given rise to a state of emergency and changes in the performance of the scientific, healthcare, social and geopolitical actors, generating drastic changes in clinical care protocols due the high transmissibility of the disease. Notwithstanding the low morbidity and mortality of the infection, it has led of the collapse of healthcare systems. Currently there is no specific pharmacological therapy that may be used as prophylaxis for COVID-19, and it is uncertain when a vaccine will be available, although there are clinical trials underway.^{1,2}

It is well known that patients with rheumatic diseases have a higher risk of moderate to severe infectious manifestations; consequently, there is a higher mortality associated with the infection due to the immunosuppression from the activity of the disease, immunosuppressive therapy and other comorbidities.^{1,3,4} However, there is no conclusive evidence yet about whether rheumatic patients have the same or increased risk of complications than the general population; this question may be answered based on the medical records of rheumatology patients with COVID-19.^{5,6}

In accordance with the scientific evidence, antimalarial agents (chloroquine and hydroxychloroquine), normally used as immunomodulators in rheumatoid arthritis, systemic lupus erythematosus and other systemic autoimmune diseases,^{7,8} have shown to decrease the viremia *in vitro* against SARS-CoV and SARS-CoV-2,^{9,10} and clinical trials have shown a reduction in the viral shedding time; moreover, there are a number of protocols currently being developed to show its efficiency in improving the clinical outcomes (severity or progression).^{11,12} An opened, non-randomized clinical trial shows that that treatment with hydroxychloroquine is associated with a significant reduction or elimination of the viral load in patients with COVID-19, and its effect may be reinforced by the addition of azithromycin.¹² Likewise, *in vitro* hydroxychloroquine was found to be more potent than chloroquine.¹³

Nowadays, chloroquine and hydroxychloroquine are among the few therapeutic options available to use in severe forms of COVID-19,^{11,12,14} and are being considered for inclusion in the treatment guidelines of the SARS-CoV-2 infection by the national health commissions of countries such as China, Spain, Italy, The United States, and Colombia.^{3,9,15} However, its role in prophylaxis is still being debated¹¹; only time and the ongoing clinical trials may be able to clarify its prophylactic or therapeutic role and its effect on the risk of progression or mortality due to COVID-19.

The role of some immunosuppressants such as tocilizumab, anakinra, adalimumab and small molecules has also been discussed for improving the clinical results of COVID-19-associated pneumonia.^{16–19}

Therefore, there is an impending risk of shortages of the antimalarial agents hydroxychloroquine and chloroquine,²⁰ in addition to the immunosuppressors (tocilizumab, anakinra, adalimumab and small molecules). As a result of this situation, the purpose of this review is to submit some general clinical and administrative recommendations on the management of outpatients with autoimmune or systemic inflammatory disease, in the context of the COVID-19 pandemic, and its potential consequences, such as shortages of the medications used in the normal practice of rheumatology.

It is important to highlight that although there is no conclusive scientific-clinical evidence for the therapeutic substitution of antimalarial and immunosuppressive agents, these recommendations are also based on the guidelines by experts in rheumatology and infectious diseases, pursuant to the current indications of the various scientific societies.

Objective

To make general, clinical and administrative recommendations, based on the opinion of a group of experts on the management of outpatients with autoimmune or systemic inflammatory disease, in the context of the COVID-19 pandemic, as well as the consequences it may have, such as

shortages of the drugs used in the usual practice of rheumatology.

Methodology

A narrative review of the literature associated with research was conducted on the PubMed electronic database and on the gray literature in Google. The search strategy which ended on April 29 of this year was based on MeSH terms and free language considering synonyms, abbreviations, spelling variations and plurals. The MeSH terms used in PubMed were: (*rheumatology* [MeSH Terms] OR *rheumatology* [All Fields]) AND (*COVID-19* [All Fields] OR *severe acute respiratory syndrome coronavirus 2* [Supplementary Concept] OR *severe acute respiratory syndrome coronavirus 2* [All Fields] OR *2019-nCoV* [All Fields] OR *SARS-CoV-2* [All Fields] OR *2019nCoV* [All Fields] OR (*Wuhan* [All Fields] AND (*coronavirus* [MeSH Terms] OR *coronavirus* [All Fields])) AND 2019/12[PDAT]: 2030[PDAT])). The limiting criteria for the search were articles published over the past 5 years in Spanish, English, Portuguese or French.

A review of all the documents identified and considered adequate, in addition to the publications by the Colombian, Spanish, Chilean and Argentinian societies of rheumatology was conducted. With the information collected, a scientific report, based on the most relevant evidence, was prepared. Finally, a multidisciplinary work team of methodological experts (epidemiologists) and experts on the topic (rheumatologists and specialists in infectious diseases) conducted two virtual surveys, and the final review of the recommendations and elements identified in the literature review. The work team described the recommendations submitted in this document as essential recommendations. In summary, this is the opinion of a group of experts, based on a narrative review of the specialized literature.

Target population

Adult patients (>18 years) with autoimmune or systemic inflammatory disease:

- a In remission or having achieved the treatment target.
- b Active disease or failure to achieve the treatment target.
- c With good overall prognosis (absence or few poor prognostic factors).
- d With overall poor prognosis (high risk of systemic or extra-articular involvement, difficult to manage disease, polypharmacy, marked immunosuppression, functional involvement (elevated HAQ), limited economic resources, low level of education).

General recommendations in the context of the COVID-19 pandemic

- 1 Currently there is no scientific evidence that patients with rheumatic diseases, or patients receiving immunomodulators, benefit from discontinuing the immunosuppressive therapies (disease modifying anti-rheumatic

drugs [DMARD], conventional synthetic agents, biologics and small molecules), with prophylactic intention against COVID-19, neither that their use will protect them. The current recommendation is to continue treatment unchanged, unless the patient presents symptoms of COVID-19 or other infection. In that case, the recommendation is to consult with the emergency department of the corresponding healthcare provider and determine the risk.^{1,21-23}

- 2 In patients who ask to postpone or discontinue the conventional immunosuppressor therapy or biologics, the recommendation is to discuss with them the risks and benefits of such decision.²²
- 3 In patients who are COVID-19 negative, the recommendation is to continue with corticosteroid therapy unchanged.¹
- 4 It is recommended that the rheumatologist should inquire about any comorbidities of patients with higher risk of developing complications in case of COVID-19 infection (diabetes, cardiovascular disease [hypertension, stroke], HIV, cancer, use of corticoids or immunosuppressors, chronic obstructive pulmonary disease [COPD] malnutrition [obesity and undernourishment], smokers), and whether they have developed or present any COVID-19 symptoms over the past three days (fever above 38°C, coughing, shortness of breath, anosmia and ageusia).
- 5 In patients with active arthropathy or failure to achieve the treatment goal, with respiratory symptoms or medical condition suggestive of COVID-19, that require starting biologic therapy or small molecules, the recommendation is to rule out active infection with a rapid test (if the time of evolution of symptoms is ≥ 11 days) or RT-PCR (if the time of evolution of symptoms is less than 11 days, or after 7 days of an asymptomatic patient with unprotected exposure).²⁴ In case of epidemiological linkage, the recommendation is 14-days of observation and isolation as of the time of exposure and if symptoms develop, study the case. If active infection is ruled out, the recommendation is to initiate treatment, preferably with short half-life drugs, because if infection presents, this will allow for rapid serum clearance of the immunosuppressor agent.
- 6 In patients with active arthropathy or unachieved treatment goal, with no respiratory symptoms or epidemiological contact with COVID-19, that require initiation of biologic therapy or small molecule, diagnostic tests for COVID-19 are not necessary and treatment may be initiated immediately, preferably with short half-life drugs, so if an infection presents, this will allow for rapid serum clearance of the immunosuppressor drug.
- 7 Given the high transmission of COVID-19, it is important to minimize the exposure to the virus of patients with rheumatic diseases under biologic or immunosuppressor therapy. The recommendation is that these patients should be assessed, if possible, remotely (telephone, tele-medicine, videoconference, inter alia). It is recommended to administer the medications at home or via self-medication in case of subcutaneous and intravenous therapy, unless it is the first infusion or when any risk

is involved that requires monitoring or previous medical assessment.^{3,21,22,25}

- 8 Rheumatological patients, regardless of the type of treatment, who receive biologics or immunosuppressors, shall implement the general measures recommended by the local and national health authorities regarding social distancing, use of facemasks, quarantine, hand hygiene, avoid touching the mouth, nose and eyes, and covering the mouth and nose with the elbow or a disposable handkerchief (which should be disposed of and not kept inside the pocket, with immediate hand wash) when coughing or sneezing, and in case of infection, avoid close contact with other people.^{3,21,22,26,27}
- 9 If the rheumatological patient lives with someone who has been exposed to, or presents symptoms of, COVID-19, and could be infected, the recommendation is to avoid contact with that person in the house, adopting all the isolation measures (maintain a two-meter distance), hygiene, countertop sanitation, and all the necessary cleaning measures.³
- 10 If during a medical consult the patient presents respiratory symptoms, or there is a risk of COVID-19, using a facemask shall be mandatory and refer immediately to the health-care provider for re-assessment, study and confirmation of the case.³
- 11 The continued use of antihypertensives therapy is recommended in patients who need the medication, since there is no conclusive evidence that the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB-II) is associated with a higher risk of severity or worse hospital prognosis in patients with or without COVID-19. These hypothesis are the result of observations of *in vitro* models and animal trials, since just as the coronavirus-associated severe acute respiratory virus (SARS), COVID-19 binds to the angiotensin-2 converting enzyme (ACE-2) to infect the cells and this enzyme is apparently overexpressed in ACE or ARB-II-treated subjects.²⁸⁻³¹
- 12 It is highly advisable to encourage vaccination against influenza and pneumococci, in accordance with the current recommendations. Strong recommendation in favor.³
- 13 For the adult population, the recommendation is to promote vaccination by risk groups, in accordance with the current recommendations. Strong recommendation in favor.³
- 14 No recommendation is given in favor or against the use of tocilizumab.³
- 15 It is recommended to postpone for 14 days the administration of the next dose of medication in patients receiving biologics and who are asymptomatic but have been in close contact with a patient with proven COVID-19 infection.³
- 16 In patients with stable disease, using IV biologics, it is possible to consider switching to subcutaneous administration (tocilizumab, abatacept, belimumab, evaluate infliximab to another anti-TNF), or if the patient has achieved the therapeutic target for over six months, it is possible to consider a dose reduction extending the time between doses and hence reduce the exposure to the virus.³²

Recommendations for rheumatological patients with COVID-19

- 1 Patients with autoimmune arthropathies who are diagnosed with COVID-19 may continue treatment with hydroxychloroquine and sulfasalazine.³³
- 2 It is recommended to optimize the dose of glucocorticoids as low as possible, including inhaled steroids, because of the risk of systemic or local immunosuppression in patients with documented COVID-19 infection.^{1,25,34}
- 3 The use of non-steroidal anti-inflammatory agents (NSAIDs) or selective cyclooxygenase 2 inhibitors (COX2) such as ibuprofen, naproxen, diclofenac, celecoxib, *inter alia*, as first line therapy for the management of COVID-19 symptoms is not recommended, since worse outcomes were observed when used by COVID-19 infected patients, in accordance with the reports from scientific communities. Consequently, the recommendation is to use acetaminophen in these patients, because it is a safer drug. This recommendation is not evidence-based and has been discussed by the regulatory and scientific agencies.^{22,35-37}
- 4 In the treatment of confirmed COVID-19 patients, the use of chloroquine and hydroxychloroquine is recommended, according to the severity of patients with no contraindications for its use, with caution in patients with cardiovascular comorbidities, based on the risk of QT interval prolongation and fatal arrhythmias.^{3,12,38}
- 5 If a patient has confirmed COVID-19, biologic DMARD treatment should be discontinued (individually assessing the risk-benefit) and consult his/her treating rheumatologist.³³ In patients with good response, the recommendation is to reinstate the biologic therapy after four weeks, and in patients with severe presentations, the administration of the biologic should be postponed until the infection resolves, and making sure that there will be no risk of relapse or reinfection.³
- 6 It is recommended to continuously assess for adverse reactions to medications and drug interactions in patients that need additional treatment for their underlying condition due to COVID-19 infection.
- 7 It is recommended to avoid making changes to the antiretroviral treatment regimens in patients with human immunodeficiency virus (HIV) and COVID-19. Strong recommendation in favor.³
- 8 In patients with active arthropathy or failure to accomplish the treatment goal, with resolution of the COVID-19 infection, who need to start biologic therapy or small molecule, the recommendation is to begin the administration of one of these drugs, regardless of the half-life of the medication, based on the specialist judgement.

Recommendations in case of shortage of antimalarial agents because of severe COVID-19 infection

If based on scientific evidence, there is proof that antimalarial agents are effective and safe for the prophylactic and therapeutic management of COVID-19, and antimalarial agents are included in the management guidelines of the dis-

ease, resulting in shortages thereof, under *extreme emergency*, according to the opinion of experts, the recommendations are:

- 1 Always consult the treating rheumatologist to individualize treatment changes and receive all the relevant information.
- 2 Patients with autoimmune systemic diseases shall be prioritized (systemic lupus erythematosus, systemic vasculitis, inflammatory myopathies) and those with antimalarial therapy, or at risk of systemic involvement, or other poor prognostic factors. The discontinuation of antimalarial agents is not recommended for this group of patients, since it may increase the risk of a flare-up of their underlying condition, with life-threatening consequences.
- 3 In patients with rheumatoid arthritis, it is possible to discontinue the antimalarial drugs and adjust their therapy with other DMARDs, both conventional synthetic agents or biologics, and even glucocorticoids in case of an outbreak. The strength of antimalarial agents in this disease is low and they are commonly used as adjuvant therapy.
- 4 In patients with arthropathies and systemic autoimmune diseases that have reached their therapeutic targets for extended periods of time, and have a good overall prognosis, it may be possible to reduce the dose or discontinue treatment under close observation, with the exception of patients with systemic lupus erythematosus.

Recommendation in case of shortages of tocilizumab, adalimumab and small molecules due to severe COVID-19 infection management

In accordance with the evidence, there could be a shortage of these drugs because of their potential use for the treatment of COVID-19. If this were the case, the recommendation is that the treating rheumatologist considers treatment options, and if necessary, to submit the case to the consideration of a rheumatology board meeting.

- According to the scientific evidence, tocilizumab could be associated with improved clinical results in COVID-19-associated pneumonia, reducing systemic inflammation, improving the survival rate, hemodynamics and respiratory distress. The Chinese, Italian and Spanish guidelines have included this agent in their recommendations for the treatment of COVID-19.^{1,17,19}
- A suggested potential option for the treatment of COVID-19 is adalimumab and a randomized clinical trial has been already registered.^{1,19,39}
- Scientific reports indicate that baricitinib may be a potential therapy for COVID-19-associated acute respiratory disease. It is believed that the therapeutic doses of this drug are enough to inhibit the adaptor associated kinase-1 (AAK1), and hence it could be useful in these patients; however, further studies are needed to confirm this finding. Until this date, it has not yet been included in any clinical guidelines for the management of COVID-19 patients.^{1,18,19}

Conclusions

Colombia is a developing country, with limited healthcare resources. Contingency plans must be in place to face an emergency such as the current pandemic. The purpose of this review was to identify the general recommendations for outpatient management of individuals with rheumatological diseases in the context of the COVID-19 pandemic, as well as its potential implications regarding shortages of drugs commonly used for their treatment, keeping in mind the increased complexity of these patients due to the risk of worse outcomes in the presence of infections.^{1,3,4} Some of the agents currently suggested for the treatment of COVID-19 are chloroquine and hydroxychloroquine, tocilizumab, adalimumab and baricitinib, which are currently used in rheumatological patients.^{1,9,10} However, the current evidence is not conclusive regarding their role in the prophylaxis or treatment of moderate to severe manifestations of COVID-19. Nevertheless, tocilizumab could impact the severe manifestations of COVID-19, because of interleukin inhibition, when the condition is compatible with cytokine storm.

Notwithstanding the evidence identified, there is a need to constantly review and update such evidence to adapt to the needs of the pandemic and the national healthcare system. The world emergency due to COVID-19 demands huge efforts in the search for answers to manage patients with chronic, high impact conditions. In the framework of the pandemic, the scientific evidence is constantly changing, and requires updating of the management protocols supported by increasingly robust and conclusive evidence.

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REFERENCES

1. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: faraway, so close! *Autoimmun Rev*. 2020;19:1–7, <http://dx.doi.org/10.1016/j.autrev.2020.102523>.
2. Indian Council of Medical Research. Recommendation for empiric use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection; 2020.
3. Asociación Colombiana de Infectología, Instituto de Evaluación Tecnológica en Salud (IETS). Consenso colombiano de atención, diagnóstico y manejo de la infección por SARS COV-2/COVID-19 en establecimientos de atención de la salud. *Infectio*. 2020;24:1–102.
4. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. *Liver Transplant*. 2020;26:832–4, <http://dx.doi.org/10.1002/lt.25756>.
5. Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis*. 2020;79:667–8, <http://dx.doi.org/10.1136/annrheumdis-2020-217424>.

6. The COVID-19 Global Rheumatology Alliance. The global rheumatology community's response to the worldwide COVID-19 pandemic. Available from: <https://rheum-covid.org/about/>.
7. Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica sulfato de hidroxycloquina; 2018. p. 1–11.
8. Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica difosfato de cloroquina; 2016. p. 1–10.
9. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *Int J Antimicrob Agents*. 2020;55:105923, <http://dx.doi.org/10.1016/j.ijantimicag.2020.105923>.
10. Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020;55:105932, <http://dx.doi.org/10.1016/j.ijantimicag.2020.105932>.
11. Asociación Colombiana de Infectología (ACIN). Comunicado: sobre el potencial uso de cloroquina como "profilaxis" para COVID-19. Bogotá: ACIN; 2020.
12. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020, <http://dx.doi.org/10.1016/j.ijantimicag.2020.105949>.
13. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020;2, <http://dx.doi.org/10.1093/cid/ciaa237>.
14. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv*. 2020, <http://dx.doi.org/10.1101/2020.03.22.20040758>.
15. Figueroa-Parra G, Aguirre-García GM, Gamboa-Alonso CM, Camacho-Ortiz A, Galarza-Delgado DA. Are my patients with rheumatic diseases at higher risk of COVID-19? *Ann Rheum Dis*. 2020;79:839–40, <http://dx.doi.org/10.1136/annrheumdis-2020-217322>.
16. Ferro F, Elefante E, Baldini C, Bartoloni E, Puxeddu I, Talarico R, et al. COVID-19: the new challenge for rheumatologists. *Clin Exp Rheumatol*. 2020;38:175–80.
17. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A*. 2020;117:10970–5, <http://dx.doi.org/10.1073/pnas.2005615111>.
18. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395:e30–1, [http://dx.doi.org/10.1016/S0140-6736\(20\)30304-4](http://dx.doi.org/10.1016/S0140-6736(20)30304-4).
19. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin Exp Rheumatol*. 2020;38(2):337–42.
20. El País. La paranoia provoca el desabastecimiento de fármacos contra el coronavirus. Available from: <https://elpais.com/ciencia/2020-03-25/la-paranoia-provoca-el-desabastecimiento-de-farmacos-contra-el-coronavirus.html>.
21. European League Against Rheumatism (EULAR). EULAR Guidance for patients COVID-19 outbreak. Available from: https://www.eular.org/eular_guidance_for_patients.covid19_outbreak.cfm.
22. Cadena SER. El coronavirus COVID-19 y los pacientes con enfermedades reumáticas. Available from: <https://www.ser.es/el-coronavirus-covid-19-y-los-pacientes-con-enfermedades-reumaticas/>.
23. Grupo Panamericano contra el Reumatismo. Coronavirus y enfermedades reumáticas. PANLAR; 2020. Available from: <https://www.panlar.org/pacientes/coronavirus-y-enfermedades-reumaticas>.
24. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections - the state of the art. *Emerg Microbes Infect*. 2020;9:747–56, <http://dx.doi.org/10.1080/22221751.2020.1745095>.
25. American College of Rheumatology. COVID-19 Clinical guidance for patients with rheumatic diseases. Available from: <https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-Patients-with-Rheumatic-Diseases.pdf>.
26. World Health Organization (WHO). Coronavirus. Available from: https://www.who.int/health-topics/coronavirus#tab=tab_1.
27. Fondo de las Naciones Unidas para la Infancia (Unicef). Coronavirus (COVID-19): lo que los padres deben saber. Available from: <https://www.unicef.org/es/coronavirus/lo-que-los-padres-deben-saber>.
28. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med*. 2020;382:1653–9, <http://dx.doi.org/10.1056/NEJMSr2005760>.
29. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med*. 2020;46:586–90, <http://dx.doi.org/10.1007/s00134-020-05985-9>.
30. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8:e21, [http://dx.doi.org/10.1016/S2213-2600\(20\)30116-8](http://dx.doi.org/10.1016/S2213-2600(20)30116-8).
31. Agencia Española de Medicamentos y Productos Sanitarios. Medicamentos antihipertensivos que actúan sobre el sistema renina angiotensina e infección por COVID-19. Available from: <https://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano-3/seguridad-1/2020-seguridad-1/medicamentos-antihipertensivos-que-actuan-sobre-el-sistema-renina-angiotensina-e-infeccion-por-covid-19/>.
32. National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders. Available from: <https://www.nice.org.uk/guidance/ng167>.
33. Macchine D. Clinical guide for the management of cancer patients during the coronavirus pandemic. University Hospitals Birmingham NHS Foundation Trust. Available from: <https://www.uhb.nhs.uk/coronavirus-staff/downloads/pdf/CoronavirusCancerManagement.pdf>.
34. Macchine D. Clinical guide for the management of rheumatology patients during the coronavirus pandemic. University Hospitals Birmingham NHS Foundation Trust. Available from: <https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/clinical-guide-rheumatology-patients-v2-08-april-2020.pdf>.
35. RheumNow. Rheumatology News & Information. Rheumatic disease drugs and COVID-19. Available from: <http://rheumnow.com/content/rheumatic-disease-drugs-and-covid-19>.
36. Day M. Covid-19: European drugs agency to review safety of ibuprofen. *BMJ*. 2020;368:m1168, <http://dx.doi.org/10.1136/bmj.m1168>.

-
37. Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. *BMJ*. 2020;368:1, <http://dx.doi.org/10.1136/bmj.m1086>.
 38. Massachusetts General Hospital. COVID-19 Treatment Guidance. Available from: <https://www.massgeneral.org/news/coronavirus/treatment-guidance>.
 39. Haga S, Yamamoto N, Nakai-Murakami C, Osawa Y, Tokunaga K, Sata T, et al. Modulation of TNF- α -converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-production and facilitates viral entry. *Proc Natl Acad Sci U S A*. 2008;105:7809-14, <http://dx.doi.org/10.1073/pnas.0711241105>.