Managing patients with rheumatic diseases during the COVID-19 pandemic: The French Society of Rheumatology answers to most frequently asked questions up to May 2020

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Abstract:

Background. Rheumatologists must contend with COVID-19 pandemic in the management of their patients and many questions have been raised on the use of both anti-inflammatory drugs and disease-modifying anti-rheumatic drugs (DMARD). The French Society of Rheumatology (SFR) selected the most critical ones to the daily practice of a rheumatologist and a group of 10 experts from SFR and Club Rheumatism and Inflammation (CRI) boards proposed responses based on the current knowledge of May 2020.

Basic procedure. Following the availability of the first 18 questions and statements, 1400 individuals consulted the frequently asked questions between the March 31, 2020 and April 12, 2020. As a result, 16 additional questions were forwarded to the SFR, and answered by the board. An additional round of review by email and video conference was organized, which included updates of the previous statements. The scientific relevance of 5 of the questions led to their inclusion in this document. Each response received a final assessment on a scale of 0–10 with 0 meaning no agreement whatsoever and 10 being in complete agreement. The mean values of these votes for each question are presented as the levels of agreement (LoA) at the end of each response. This document was last updated on April 17, 2020.

Main findings. Based on current scientific literature already published, in most circumstances, there is no contraindication to the initiation or continuation of anti-inflammatory drugs as well as DMARDs. If signs suggestive of infection (coronavirus or other) occurs, treatments should be discontinued and resumed, if necessary, after 2 weeks without any symptoms. Only, some signals suggest that people taking an immunosuppressive dose of corticosteroid therapy are at greater risk of developing severe COVID-19. Intra-articular injections of glucocorticoids are allowed when there is no reasonable therapeutic alternative, and providing that precautions to protect the patient and the practitioner from viral contamination are adopted, included appropriate information to the patient.

Principal conclusions. Currently available data on managing patients with rheumatic diseases during the COVID-19 pandemic are reassuring and support continuing or initiating symptomatic as well as specific treatments of these diseases, the main target of their management remaining their appropriate control, even during this pandemic.

Keywords: COVID-19, inflammatory rheumatic diseases, treatment, health system

1. Introduction

The global pandemic of COVID-19 has suddenly changed our medical practice regardless of our specialty. In particular, rheumatologists must contend with this viral infection in the management of their patients and many questions have been raised on the use of both anti-inflammatory drugs and disease-modifying anti-rheumatic drugs (DMARD) (1). On one hand, anti-inflammatory drugs and DMARD are necessary for keeping inflammatory chronic diseases or painful and crippling degenerative diseases under control and, on the other hand, are of concern for increasing the risk of COVID-19 among patients with rheumatic diseases. Paradoxically, emerging scientific literature reports a potential use of certain DMARDs in the prevention or the treatment of COVID-19 (2, 3). Currently, there is little evidence to support that patients under chronic immunosuppressive therapy are at higher risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (4).

The French Society of Rheumatology (SFR) collected questions sent to its secretariat from the beginning of the COVID-19 pandemic through March 27, 2020. A group of 10 experts from the board of the SFR and the President of the Club Rheumatism and Inflammation (CRI) selected an initial list of 18 questions that were considered the most critical to the daily practice of a rheumatologist. While considering the rapidly evolving nature of COVID-19, the proposed responses were based on the current knowledge. Any questions directly related to professional practice were excluded and directed to the National Union of Rheumatologists.

We hope that these questions and their answers, will be considered beneficial for our community and other medical fields that utilize these drugs. The following questions are related to the treatment and palliative care of patients during the COVID-19 pandemic.

2. Methods

Questions and drafted statements were reviewed and assessed using the modified Delphi method until a consensus was reached among the group. The entire panel completed two rounds of review by email and one video conference.

Following the availability of the first 18 questions and statements, 1400 individuals consulted the frequently asked questions between the March 31, 2020 and April 12, 2020. As a result, 16 additional questions were forwarded to the SFR, and answered by the board. An additional round of review by email and video conference was organized, which included updates of the previous statements. The scientific relevance of 5 of the questions led to their inclusion in this document. Each response received a final assessment on a scale of 0–10 with 0 meaning no agreement whatsoever and 10 being in complete agreement. The mean values of these votes for each question are presented as the levels of agreement (LoA) in the table 1. This document was last updated on April 17, 2020.

3. Results: Answers to most asked questions (table 1)

3.1. How should painkillers be prescribed?

In patients already treated with analgesics, those taking major analgesics should be carefully monitored for the potential risk of respiratory depression and disorientation, which may be signs of COVID-19 infection.

In the case of poorly tolerated fever or pain in the context of COVID-19 or other respiratory virus, treatment is based on paracetamol, not to exceed 60 mg/kg per day and 3 g per day.

There is no benefit to combining paracetamol with nonsteroidal anti-inflammatory drugs (NSAIDs), nor to prescribing paracetamol continuously rather than on demand (5). Due to the potential hepatic side effects, paracetamol on demand is preferred.

3.2. Can non-steroidal anti-inflammatory drugs (NSAIDs) be prescribed?

At this time, there is no contraindication to prescribing an NSAID unless the patient has symptoms suggestive of COVID-19. If the patient is already taking NSAIDs and cannot do without (e.g., spondyloarthritis), there is also no contraindication to continuing treatment. However, if symptoms suggestive of COVID-19 are present, it is recommended that treatment be discontinued. The treatment will be resumed, if necessary, after 2 weeks without any symptoms.

3.3. Is there an excess risk of complications with ACE inhibitors and ARBs?

Conflicting data has been initially published on both an aggravating or protective role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with COVID-19 (6).

Based on the current information, the European Society of Cardiology (7) and the American Heart Association (8) have published statements urging physicians and patients to continue use of these medications to control hypertension in the context of the pandemic.

Recent studies on large population did not confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs with death in COVID-19 context (9, 10).

3.4. What is the opinion of general corticosteroid therapy?

Despite the absence of data in the literature but given the available data on the presumed risk of other respiratory infections, the French High Council of Public Health considers that people taking an immunosuppressive dose of corticosteroid therapy (≥ 10 mg per day for more than 2 weeks) are at greater risk of developing severe COVID-19. The additional risk supports seeking a minimum effective dose of oral corticosteroids, if possible, ≤ 10 mg per day.

If infection occurs, corticosteroid therapy should not be stopped abruptly because of the risk of adrenal insufficiency. High-dose corticosteroid therapy was tested during the SARS-CoV and Middle East respiratory syndrome (MERS)-CoV outbreaks, with inconclusive results (11) and is currently being tested in clinical trials on COVID-19. A recent meta-analysis assessing the effects of corticosteroid treatment on patients with coronavirus infection reported that patients with severe conditions were more frequently treated by corticosteroids that non-critical patients. However, corticosteroid use was associated with an increased mortality and serious adverse reactions (12).

3.5. Is it possible to carry out local joint injections?

With many limitations on movement within and around regions as well as stay-at-home restrictions during the COVID-19 pandemic, an intra-articular injection of

glucocorticoids is allowed when there is no reasonable therapeutic alternative, and with the following considerations:

- The risk of contamination by moving the patient to a medical facility;
- Precautions to protect the patient and the practitioner from viral contamination, in addition to the usual aseptic measures;
- The absence of associated risk factors for severe COVID-19 and informing the patient of the potential increased risks and obtaining consent.

3.6. How could hydroxychloroquine be useful for COVID-19?

Hydroxychloroquine has antiviral properties demonstrated *in vitro* (13). However, currently there is no proof of its clinical effectiveness for prevention or cure (14). Some preliminary data on a small number of patients were published on April 17, 2020. Unfortunately, a conclusion could not be obtained due to issues with methodology (15). Recent observational studies did not find any differences in in-hospital mortality (16, 17). Therefore, it is not currently recommended to prescribe hydroxychloroquine either as monotherapy or in combination with azithromycin outside of supervised clinical trials.

3.7. Can conventional synthetic background treatments (e.g., methotrexate, leflunomide, sulfasalazine) be maintained?

It is advisable to maintain background treatments if they are effective and well tolerated, in order to avoid the potential occurrence of a flare-up. However, patients should be advised to practice preventative measures to reduce the chance of being infected by SARS-CoV-2, including optimal hand hygiene, social distancing, covering of the mouth and nose with the inside of the elbow or with a disposal tissue when coughing or sneezing, and

throwing used tissues in the trash) (18). If symptoms suggestive of COVID-19 occur, background therapy should be withheld, and any corticosteroids should be maintained. However, there is currently no published data on the potential risks or benefits to continue or stop the background therapy in patients with COVID-19.

3.8. Is it possible to initiate a conventional synthetic background treatment (e.g., methotrexate) in a patient with early onset rheumatic diseases?

There is no contraindication to initiating a conventional synthetic background treatment in order to control the level of rheumatic disease activity. Therefore, patients should be advised to practice preventative measures. In the event of symptoms suggestive of COVID-19, background treatments should be suspended, and corticosteroids should be maintained if they have been prescribed simultaneously.

3.9. Can colchicine be prescribed?

Colchicine treatment may be prescribed during the COVID-19 pandemic, as there is no data suggesting a risk of severe complications. However, preventative measures should be followed in order to lessen the chance of SARS-CoV-2 infection.

If symptoms suggestive of COVID-19 occur, discontinuation of treatment should be discussed. While some autoinflammatory diseases warrant continued administration of colchicine (for example, to prevent a gout attack), patients should be monitored for possible drug interactions. Furthermore, there may be an overlap in symptoms of COVID-19 or drug side effects. For example, diarrhea is commonly observed with COVID-19 but may also result from an overdose of colchicine.

Of note, as of April 17, 2020, five studies testing the effects of colchicine on COVID-19 were available on ClinicalTrials.gov (NCT04350320, NCT04326790, NCT04328480, NCT04322565, NCT04322682).

3.10. Can JAK inhibitors (baricitinib and tofacitinib) be maintained or initiated?

In the current context, there is no contraindication to the initiation or continuation of a janus kinase inhibitor (JAKi). If signs suggestive of infection (coronavirus or other) occurs, treatment should be discontinued. In addition, *in vitro* data are available that demonstrate antiviral activity of baricitinib (19, 20).

Currently, no data exists on the risk or benefit to continue or stop a JAKi in patients with COVID-19. Only one open-label pilot study on 12 patients suggests a potential benefit of baricitinib combined with lopinavir-ritonavir in COVID-19 (21). Furthermore, on April 17, 2020, six studies testing the effects of JAKi on COVID-19 were available on ClinicalTrials.gov (baricitinib: NCT04340232, NCT04346147, NCT04320277, NCT04345289, NCT04321993; tofacitinib: NCT04332042; ruxolitinib: NCT04348071, NCT04334044, NCT04338958, NCT04337359, NCT04331665, NCT04348695).

3.11. Are anti-interleukin-6 receptor therapies beneficial to patients with severe COVID-19?

The occurrence of acute respiratory distress patterns on day 8-10 of COVID-19 are associated with the so-called cytokine storm and other inflammatory responses that may resemble macrophage activation syndrome.

One of the first open studies in China supported the potential efficacy of interleukin-6 (IL-6) blockade, notably by tocilizumab (TCZ) (22). In another study by Luo et al. (23), there is less confidence in the use of TCZ since 3 of the 15 patients treated in open-label studies died. Results from recent studies are encouraging (24, 25), but data from randomized control trials are expected.

As of April 17, 2020, there are 30 studies on ClinicalTrials.gov concerning the potential use of TCZ or other anti-IL6 therapies (sarilumab, siltuximab, sirukumab, and clazakizumab).

The Italian phase 2 study entitled TOCIVID-19 (NCT04317092) proposes 2 infusions of TCZ at 8 mg/kg 12 hours apart. The COVACTA (NCT04320615) study is a phase 3, randomized, double-blind, placebo-controlled study. A phase 2 study in Denmark (NCT04320615) has planned to include 330 patients (a single infusion at 8 mg/kg). A phase 2 study in Denmark (NCT04322773) has planned to include 200 patients in 4 arms including one intravenous TCZ arm and one subcutaneous TCZ arm compared to sarilumab and control. The Swiss study CORON-ACT (NCT04335071) has planned to include 100 patients. Finally, the French study CORIMUNO plans to test different biological DMARDs (bDMARD), including tocilizumab (CORIMUNO-TOCI; NCT04331808).

Sarilumab has been evaluated in at least 5 studies including the specific CORIMUNO-SARI arm (NCT04324073). A large international phase 2 and phase 3 study (NCT04315298) has planned to include 400 patients (severe or critical forms of COVID-19) and will test the efficacy of sarilumab at a high and low intravenous dose.

For siltuximab, there is one Italian retrospective study (NCT04322188) and one Spanish phase 2 study (NCT04329650) with open-label treatment of 100 patients who will receive one intravenous injection at 11 mg/kg.

There is one study evaluating the efficacy of sirukumab in severe COVID-19 with acute respiratory distress.

3.12. Can biological targeted treatments be maintained or initiated?

It is advisable to maintain bDMARD if effective and well tolerated, while also practicing preventative measures in order to avoid the potential occurrence of an outbreak. If symptoms are suggestive of COVID-19 infection, bDMARD should be withheld, and corticosteroids if prescribed, should be maintained. Initiation of a bDMARD should be decided on a case-by-case basis according to the inflammatory activity of the disease and the informed consent of the patient(s).

Currently, there is no data in the medical literature to suggest additional risk or benefit to continuation or elimination of bDMARD in patients infected by SARS-CoV-2.
Furthermore, on April 17, 2020, multiple studies testing the effects of anti-IL-1, anti-IL-6, anti-TNF and other bDMARD on COVID-19 were available on ClinicalTrials.gov (see question 17).

3.13. Can anti-interleukin-1 (anakinra / canakinumab) therapy be maintained or initiated?

It is advisable to maintain bDMARD, and in particular anti-interleukin-1, if effective and well tolerated while also practicing preventative measures, in order to avoid the potential occurrence of a SARS-CoV-2 infection.

If there are any symptoms suggestive of COVID-19, discontinuation of treatment should be discussed. Some indications, such as Still's disease, can make it extremely complicated to stop treatment, and therefore require expert medical advice.

For the initiation of anti-interleukin-1 (IL-1) therapy, the decision should be made on a case-by-case basis according to the pathology and inflammatory activity, as well as the patient's informed consent.

Finally, the potential value of anti-IL-1 antibodies was discussed, along with IL-6 receptor blockers, in treating the possible cytokine storm that occurs in COVID-19 and causes acute respiratory distress syndrome (26, 27). However, this idea is currently unresolved.

At this time, there is no data in the medical literature about the risk or benefit to continue or stop a bDMARD in patients with COVID-19. Furthermore, as of April 17, 2020, six studies testing the effects of anakinra and canakinumab on COVID-19 were available on ClinicalTrials.gov (see question 17).

3.14. My patient is receiving intravenous biologics: should I consider switching to a subcutaneous form (abatacept and tocilizumab)?

In order to avoid the need for a patient to receive treatment in the hospital, where there is a high risk of contamination, switching to subcutaneous administration of abatacept and tocilizumab can be considered. Altering treatment administration will only be considered in patients who either have experience with subcutaneous administration or are able to self-administer the treatment using a syringe or pen (the need for a home-care nurse makes the option less attractive).

3.15. My patient is undergoing parenteral treatment (e.g., methotrexate, teriparatide, denosumab), should another route of administration or alternative therapy be considered?

This question is essentially raised having in mind the need for compliance with the stay-at-home restrictions, limited contact for fragile populations, and appropriate use of health care professional resources. There is no contraindication to continue these treatments. The answer depends on the molecule:

Methotrexate. The decision depends on the original reason for choosing the injectable form. If for efficacy, optimal control of the disease is necessary. If tolerance was the main reason, this may be difficult to change, however, it could be possible to test with a dose-splitting trial. If methotrexate is used as a maintenance therapy, the response to the change should be determined by the physician.

Teriparatide. Even though there is no rebound of bone cellular activities and a sustained decrease in the risk of fracture following treatment withdrawal, the biological effects are not persistent (28). It is therefore necessary to add an antiresorptive agent within 3 months. This should be discussed if the patient has received at least one year of teriparatide.

Denosumab. The adjustment period is narrow, beyond 6 months after the previous injection. This occurs because the effect quickly dissipates once the treatment is discontinued, followed by a rebound in bone remodeling, apparent within a few weeks (29). Therefore, delaying the next injection can only be discussed when the end of the stay-at-home restriction is known.

Zoledronic acid. The infusion can be postponed from one to several months (30).

3.16. Can I maintain immunomodulatory treatment (methotrexate and targeted therapies) in a patient with rheumatoid arthritis and associated lung disease?

In the absence of confirmed or suspected COVID-19, immunomodulatory therapies for rheumatoid arthritis should not be stopped, even in the context of a specific lung

involvement. To date, on April 17, 2020, there is no information on the prognosis of COVID-19 in rheumatoid lung disease.

3.17. What are the main molecules currently being tested in clinical trials?

As of April 12, 2020, the number of clinical trials listed on ClinicalTrials.gov for COVID-19 reached 689.

Not surprisingly, the first studies initiated include the use of various antiviral molecules, most commonly remdesivir, but also ritonavir, darunavir, danoprevir, favipiravir, lopinavir, oseltamivir.

There are currently more than twenty clinical studies using hydroxychloroquine, including controlled, double-blind, and placebo-controlled trials. A major phase 3 study in Germany (NCT04340544) has planned to include 2,700 patients using a daily dose of 600 mg hydroxychloroquine for 7 days with a primary endpoint of clinical resolution of mild COVID-19 at D28 ± 2. Two other studies (NCT04344457 and NCT04334512) will compare hydroxychloroquine versus azithromycin.

Prevention strategy studies should also be highlighted. The French COVIDAXIS (NCT04328285) study is a large, randomized, double-blind, phase 3, controlled study conducted in 600 exposed healthcare professionals comparing hydroxychloroquine at a dose of 400 mg on D1 and D2, then 200 mg per day versus placebo. The duration of treatment is 2 months with a primary endpoint of the occurrence of a symptomatic or asymptomatic COVID-19. Other prevention studies are also scheduled including PATCH (NCT04329923), PHYDRA (NCT04318015), SHARP (NCT04342156) and EPICOS (NCT04334928).

The Spanish study EmCOVID-HidroxiCLOROQUINA (NCT04330495) is a phase 4, randomized, double-blind, controlled study using hydroxychloroquine for chemoprophylaxis in patients with chronic inflammatory disease treated with biologics or JAK inhibitors (JAKi). A total of 800 patients diagnosed with inflammatory bowel disease, rheumatoid arthritis, seronegative spondyloarthritis, or psoriasis will be enrolled to receive 200mg HCQ twice daily for 6 months.

Other synthetic molecules under investigation include losartan, thalidomide, sildenafil, defibrotinide, fingolimod, linagliptine, ibuprofen, naproxen (for critically ill COVID-19 patients), and colchicine (see question 9).

Targeted therapies, including JAKi, are also under investigation (see question 10). An Italian prospective open-label study is evaluating tofacitinib at a dose of 10 mg twice daily for 14 days. Several studies will test the efficacy of ruxolitinib while five other studies will test baricitinib, including the phase 3 BARI-COVID study that plans to enroll 60 patients who will receive a dose of 4 mg per day for 2 weeks and be compared to a control group.

A host of biologics are also under investigation including: bevacizumab (anti-VEGF), eculizumab (anti-C5 complement), mepolizumab (anti-CD147), and 3 anti-GmCSF (mavrilimumab, gimsilumab, and lenzilumab).

With respect to anti-IL-1 therapeutics, the phase 2 study entitled ESCAPE and the arm of the CORIMUNO study: CORIMUNO-ANA (240 patients to be included) are retained (see question 13).

Finally, there are also current studies evaluating the efficacy of convalescent plasma transfusion.

Studies on anti-IL-6 drugs are the subject of a separate question (see question 11).

3.18. What is the risk of rhythm disorder under hydroxychloroquine?

The information currently conveyed in the mainstream media on hydroxychloroquine is poorly controlled (31). Much remains to be elucidated regarding cardiac events with the use of hydroxychloroquine. While hydroxychloroquine monotherapy or in combination with azithromycin presents a low risk of QT interval prolongation and torsades de pointes (TdP) ventricular tachycardia, in the case of COVID-19, the risk of TdP could be increased for multiple reasons (32):

- Self-medication and/or use of a loading dose;
- Possible cardiac involvement as a result of SARS-CoV-2 infection. Myocardial inflammation and viral particle infiltration of the myocardium have been recently described in one patient (33);
- A potential pro-arrhythmic role of inflammatory cytokines, such as IL-6 (34);
- The presence of hypokalemia;
- Multiple drug interactions (azithromycin, antiretrovirals, drugs used for resuscitation).

Cardiologists are neither for or against the use of hydroxychloroquine for COVID-19, but recommend routinely monitoring patients hospitalized for COVID-19 by electrocardiogram.

Of note, on April 10, 2020, the French Drug Safety Agency (ANSM) reported 43 cases of cardiac adverse events with hydroxychloroquine, alone or in combination (notably with azithromycin). These events have been classified to 3 categories: 7 cases of torsade de pointe, including 3 revived by defibrillation; about 10 electrocardiographic rhythm disorders or cardiac symptoms presenting as syncope; and conduction disorders including prolongation of the QT interval, with a favorable prognosis after cessation of treatment.

For systemic lupus, the data is encouraging. A French study of 75 lupus patients treated with hydroxychloroquine showed that PR and QTc intervals and heart rate were unchanged under this treatment (35). However, hydroxychloroquine can lead to QT interval

prolongation, and is therefore contraindicated in combination with citalopram, escitalopram, hydroxyzine, domperidone, and piperazine due to the risk of TdP.

3.19. What are the recommendations on cohabitation of a patient on bDMARD or JAK inhibitor with a person who has COVID-19?

The recommendations are to continue treatment in the absence of COVID-19 infection However, patients should be advised to practice preventative measures to reduce the chance of being infected by SARS-CoV-2. This includes as much isolation as possible of the person who has COVID-19 and wearing a face mask.

3.20. When should background treatment resume following recovery from COVID-19?

Currently, we do not have sufficient data to answer this question. Nevertheless, the first results of the Italian experience provide some initial insight. From a cohort of 320 chronic inflammatory rheumatic diseases treated with bDMARD or JAKi, 8 patients had a COVID-19 infection either confirmed or strongly suspected. In all cases, the authors report having suspended treatment during the infection. Treatment was resumed after a "transient" discontinuation.

Based on our experience of infectious events, particularly bacterial events under bDMARD, we could consider resuming the in-depth treatment one to two weeks after the absence of any symptoms, i.e. a total interruption of about 3 to 4 weeks.

3.21. What is the mechanism of serious respiratory and visceral involvement of COVID-19?

The severe pneumonia appearing in some subjects after a few days with COVID-19 could be due to an excessive immune response with uncontrolled pro-inflammatory cytokine release, described as a cytokine storm. Excessive cytokine release also occurs in macrophage activation syndrome (MAS). There are profound immunological similarities between the pathologies of severe pneumonia and MAS (26, 36).

For this reason, some have proposed the use of potent anti-inflammatory therapeutics such as anakinra and tocilizumab. The use of these anti-inflammatory therapeutics remains has remains an area of future research.

3.22. Should we consider screening asymptomatic people with inflammatory musculoskeletal disorders?

In France, screening by PCR is only recommended in the case of symptomatic COVID-19, which includes patients with inflammatory musculoskeletal disorders. A patient suffering from inflammatory rheumatism should be tested if symptomatic. However, it appears that the availability of the test for COVID-19 varies based on geography.

Hopefully, effective serological testing will soon be available, which would allow asymptomatic individuals to be identified. Currently, there is no information on the population that will be favored for these tests. However, the potential of antibody testing for COVID-19 is a subject of controversy (37).

3.23. What are the rheumatological and dermatological manifestations of COVID 19?

To date, there are no rheumatic manifestations of COVID-19 described in the literature. On the other hand, dermatological manifestations associated with SARS-CoV-2 infection have recently been described and can be categorized as:

- Para-viral manifestations (i.e., related to the host response in the presence of the virus and not a direct cytotoxic effect of the virus) have been described, including erythematous eruptions, generalized urticaria, and pseudovaricella. These eruptions, which mainly affect the trunk, are not very pruritic, usually heal within a few days without sequelae, and are not correlated with the severity of the disease.
- Signs of disseminated intravascular coagulation have occurred, and may be accompanied by skin involvement with acral ischemic necrosis (bullae, gangrene).
- Toxidermias in connection with supportive treatments (antibiotics, etc.), and the various antiretroviral treatments currently under investigation, including chloroquine, which can be a source of acute pruritus.
- Exacerbations of pre-existing dermatoses such as acne, rosacea have been observed. The current stress generated by the overall situation and confinement can also be a generator of dermatosis flare-ups.
- Contact dermatoses have been linked to repetitive hand washing, the wearing of gloves, masks and glasses.
- Cutaneous vasculitides have recently been described which are linked to the inflammatory load of the virus, manifesting as small red lesions that can be painful (such as frostbite) on the fingers or even dyshidrosis, a form of eczema, on the extremities.

4. Conclusion

Not only is it important to understand how to stop the spread of COVID-19, but also to understand the best way to manage patients with underlying inflammatory diseases. Although continued research is required, the questions and answers presented here represent a major step in guiding rheumatologists to provide the most optimal treatment regimen for their patients.

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T.S. reports occasional interventions for AbbVie, Biogen, Lilly, Nordic Pharma, Novartis, Pfizer, Sanofi

D.W. reports occasional interventions: AbbVie, BMS, MSD, Pfizer, Roche Chugai, Amgen, Nordic Pharma, UCB, Novartis, Janssen, Celgene, Hospira, Lilly, Sandoz, Grunenthal, and indirect interests: Abbvie, Pfizer, Roche Chugai, MSD, UCB, Mylan, Fresenius Kabi

References

1. Richez C, Lazaro E, Lemoine M, Truchetet ME, Schaeverbeke T. Implications of COVID-19 for the management of patients with inflammatory rheumatic diseases. Joint Bone Spine. 2020;87(3):187-9.
2. Quartuccio L, Semerano L, Benucci M, Boissier MC, De Vita S. Urgent avenues in the treatment of COVID-19: Targeting downstream inflammation to prevent catastrophic syndrome. Joint Bone Spine. 2020;87(3):191-3.
3. Benucci M, Damiani A, Infantino M, Manfredi M, Quartuccio L. Old and new antirheumatic drugs for the treatment of COVID-19. Joint Bone Spine. 2020;87(3):195-7.
4. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020. doi: 10.1001/jama.2020.6019.
5. Little P, Moore M, Kelly J, Williamson I, Leydon G, McDermott L, et al. Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic randomised factorial trial. BMJ. 2013;347:f6041.
6. South AM, Tomlinson L, Edmonston D, Hiremath S, Sparks MA. Controversies of renin-angiotensin system inhibition during the COVID-19 pandemic. Nat Rev Nephrol. 2020.
7. Cardiology ESo. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. https://wwwescardioorg/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang.
8. Guo J, Huang Z, Lin L, Lv J. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Viewpoint on the Potential Influence of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on Onset and Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. J Am Heart Assoc. 2020;9(7):e016219.
9. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med. 2020. doi: 10.1056/NEJMoa2006923
10. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. 2020. doi: 10.1056/NEJMoa2007621
11. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395(10223):473-5.
12. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect. 2020. doi: 10.1016/j.jinf.2020.03.062
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. doi: 10.1093/cid/ciaa237
14. Spinelli FR, Ceccarelli F, Di Franco M, Conti F. To consider or not antimalarials as a prophylactic intervention in the SARS-CoV-2 (Covid-19) pandemic. Ann Rheum Dis. 2020;79:666-7.
15. 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. 2020:105949.
16. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA. 2020.doi: 10.1001/jama.**2020**.8630

17. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020. doi: 10.1056/NEJMoa2012410
18. Publique HCdlS. https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=807.
19. 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(10223):e30-e1.
20. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020;20(4):400-2.
21. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. J Infect. 2020. doi: 10.1016/j.jinf.2020.04.017.
22. 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. doi: 10.1073/pnas.2005615117.
23. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol. 2020. doi: 10.1002/jmv.25801.
24. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev. 2020:102568.
25. Alattar R, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. J Med Virol. 2020. doi: 10.1002/jmv.25964
26. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.
27. Aouba A, Baldolli A, Geffray L, Verdon R, Bergot E, Martin-Silva N, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. Ann Rheum Dis. 2020. doi: 10.1136/annrheumdis-2020-217706
28. Eastell R, Nickelsen T, Marin F, Barker C, Hadji P, Farrerons J, et al. Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled European Study of Forsteo (EUROFORS). J Bone Miner Res. 2009;24(4):726-36.
29. McClung MR, Wagman RB, Miller PD, Wang A, Lewiecki EM. Observations following discontinuation of long-term denosumab therapy. Osteoporos Int. 2017;28(5):1723-32.
30. Grey A, Bolland MJ, Horne A, Wattie D, House M, Gamble G, et al. Five years of anti-resorptive activity after a single dose of zoledronate--results from a randomized double-blind placebo-controlled trial. Bone. 2012;50(6):1389-93.
31. Kim AHJ, Sparks JA, Liew JW, Putman MS, Berenbaum F, Duarte-Garcia A, et al. A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19. Ann Intern Med. 2020. doi: 10.7326/M20-1223.
32. Lazzerini PE, Boutjdir M, Capecchi PL. COVID-19, Arrhythmic Risk and Inflammation: Mind the Gap! Circulation. 2020. doi: 10.1161/CIRCULATIONAHA.120.047293.
33. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020. doi: 10.1002/ejhf.1828.

34. Lazzerini PE, Laghi-Pasini F, Bertolozzi I, Morozzi G, Lorenzini S, Simpatico A, et al. Systemic inflammation as a novel QT-prolonging risk factor in patients with torsades de pointes. Heart. 2017;103(22):1821-9.
35. Costedoat-Chalumeau N, Hulot JS, Amoura Z, Leroux G, Lechat P, Funck-Brentano C, et al. Heart conduction disorders related to antimalarials toxicity: an analysis of electrocardiograms in 85 patients treated with hydroxychloroquine for connective tissue diseases. Rheumatology (Oxford). 2007;46(5):808-10.
36. Pedersen SF, Ho YC. SARS-CoV-2: A Storm is Raging. J Clin Invest. 2020;130:2202-5
37. Abbasi J. The Promise and Peril of Antibody Testing for COVID-19. JAMA. 2020. doi: 10.1001/jama.**2020**.6170.

Table 1. Answers to most asked questions

	Questions	LoA
1	How should painkillers be prescribed?	9.6
2	Can NSAIDs be prescribed?	9.4
3	Is there an excess risk of complications with ACE inhibitors and ARBs?	9.7
4	What is the opinion of general corticosteroid therapy?	9
5	Is it possible to carry out local joint injections?	9.4
6	How could hydroxychloroquine be useful for COVID-19?	9.5
7	Can conventional synthetic background treatments (e.g., methotrexate, leflunomide, sulfasalazine) be maintained?	9.7
8	Is it possible to initiate a conventional synthetic background treatment (e.g., methotrexate) in a patient with early onset rheumatic diseases?	9.7
9	Can colchicine be prescribed?	9.3
10	Can JAK inhibitors (baricitinib and tofacitinib) be maintained or initiated?	9.3
11	Are anti-interleukin-6 receptor therapies beneficial to patients with severe COVID-19?	9.3
12	Can targeted biological treatments be maintained or initiated?	9.3
13	Can anti-interleukin-1 (anakinra / canakinumab) therapy be maintained or initiated?	9.6
14	My patient is receiving intravenous biologics: should I consider switching to a subcutaneous form (abatacept and tocilizumab)?	9.8
15	My patient is undergoing parenteral treatment (e.g., methotrexate, teriparatide, denosumab), should another route of administration or alternative therapy be considered?	9.6
16	Can I maintain immunomodulatory treatment (methotrexate and targeted therapies) in a patient with rheumatoid arthritis and associated lung disease?	9.5
17	What are the main molecules currently being tested in clinical trials?	9.5
18	What is the risk of rhythm disorder under hydroxychloroquine?	9.4
19	What are the recommendations on cohabitation of a patient on bDMARD or JAK inhibitor with a person who has COVID-19?	9
20	When should background treatment resume following recovery from COVID-19?	9.2
21	What is the mechanism of serious respiratory and visceral involvement of COVID-19?	9.3
22	Should we consider screening asymptomatic people with inflammatory musculoskeletal disorders?	9
23	What are the rheumatological and dermatological manifestations of COVID-19?	9.5

ACE, Angiotensin-Converting Enzyme; ARBs, Angiotensin II Receptor Blockers; DMARDs, disease-modifying antirheumatic drugs; JAK, Janus kinase; LoA, levels of agreement; NSAIDs, non-steroidal anti-inflammatory drugs