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Respiratory Medicine

Editorial

Disputes over the production and dissemination of misinformation in the time of COVID-19

A B S T R A C T

Ultimate coronavirus disease 2019 (COVID-19) mitigation and crisis resolution is dependent on trustworthy data and actionable information. At present time, there is still no cure for COVID-19, although some treatments are being used in severe illness. Regrettably, as the SARS-CoV-2 virus spreads, the lack of cure has been accompanied by an increasing amount of medical misinformation. In particular, there is a lot of misinformation about how to treat patients who have tested positive for SARS-CoV-2 and who are asymptomatic or have mild symptoms and for whom management at home is deemed appropriate. In this editorial, we highlight the risks deriving from this misinformation, which often arises from the publication of studies that are not conceptually and methodologically accurate.

1. Introduction

A recurrent question from physicians is "How should I treat my COVID-19 patients?". On the other hand the COVID-19 patients frequently ask "Can I really be cured and my life be spared?". The need to give answers to these questions leads us to believe that any proposal to improve our interfacing as physicians with COVID-19 is certainly welcome at a time when we are having difficulty fighting a pandemic that is highlighting all our organizational weaknesses.

Fortunately, the scientific community is generating huge amounts of new, practical knowledge in record time [1]. As of February 27th, 2021, Pubmed, the publications database focused on biomedicine and health sciences, returns 107,445 publications for the search term "COVID-19".

All researchers and health professionals totally agree that ultimate COVID-19 mitigation and crisis resolution is dependent on high-quality research aligned with top priority societal goals that yields trustworthy data and actionable information [2]. Regrettably, the spread of SARS-CoV-2 virus has been accompanied by a worrying amount of medical misinformation [3]. Most misinformation concerns the results of studies that were empirical in conception, and especially preliminary or inconclusive [4], although conducted in apparent good faith.

Unfortunately, social media and other communication channels often spread this misinformation [5,6] to inform a public eager to be reassured, without considering that this can result in the production of misleading information, which causes the spread of outright falsehoods. There is a real risk that such falsehoods arouse concern or, conversely, high expectations among patients unaware of the fact that their physician is diligently following international guidelines even when they are not based on solid scientific evidence, as in the case of the management of COVID-19.

The weight of misinformation is felt especially when a patient positive to the SARS-CoV-2 virus can be treated at home because he/she has a mild form or, even, is asymptomatic. Unfortunately, there are still no randomised clinical trials that can guide physicians on choosing the most suitable treatment. On the other hand, there is an urgent need to contain the epidemic and also reduce the number of hospitalized patients to alleviate the enormous workload of hospital workers caused by COVID-19.

In the absence of solid scientific evidence, physicians are often forced to trust the results of studies that are not very reliable, but which nevertheless promise a favourable outcome. On the other hand, patients or their relatives urge physicians to prescribe treatments that social media and other outlets have indicated as really effective. This rarely occurs in hospitals, but it is very common when the patient is treated at home.

2. Drugs to treat mild forms and prevent their evolution to more severe forms

With no specific COVID-19 agents available, several drugs have been proposed to treat mild forms and prevent their evolution towards more severe forms. Generally, the proposals are based on theory, on the effects of the drug on coronavirus replication in vitro, on experimental data showing SARS-CoV-2 inhibition and, sometimes, also on personal experiences gained during small spontaneous studies.

Gautret and colleagues advocated "COVID-19 patients be treated with hydroxychloroquine and azithromycin to cure their infection and to limit the transmission of the virus to other people." [7].

Another study recommended that improving vitamin D status in the general population has a potential benefit in reducing the severity of morbidities and mortality associated with acquiring COVID-19 [8].

Based on their own experience, in a short letter a groups of physicians working in Naples (Italy) proposed a home treatment for COVID-19 patients that includes the association of low molecular weight

heparin (4000 or 6000 UI each day based on weight), prednisone 25 mg in the morning and 12.5 mg in the evening and azithromycin 500 mg/ day for six days [9]. This therapeutic protocol must be started immediately after the positive molecular test (about 3–4 days on average after the onset of symptoms).

3. Methodological flaws of the studies that generated the proposals

We have taken these studies among the many published though subject to strong criticism, as an example to discuss the risk arising from disinformation when we have to treat a patient with COVID-19. Actually, these studies present several gross methodological weaknesses that substantially undermine their value.

The study of Gautret and colleagues [7] received heavy criticism. According to Rosendaal [10], there are at least ten points in the protocol of this study that are highly questionable. In particular, the choice of an open and non-randomised protocol was highlighted, where the assignment to the different groups was decided and managed by the investigator. The duration of the test also raises questions: six days against the 14 days planned looking at the registered protocol (EudraCT: 2020-000890-25). The choice of viral load in the swabs as an endpoint also questions this trial. Another limitation is the presumed presence of asymptomatic, four in the control group and two, in the treated group. Correctly it has been pointed out "Yet, the manuscript describes this as a study in hospitalized patients. It seems unlikely that asymptomatic patients were admitted to hospital".

The PLOS ONE editors [11] raised concerns on the study of Maghbooli and colleagues [8]. In particular, they highlighted that there were questions about the reported study's sample size and whether it was adequate to address the aims of the study, whether the statistical analyses and results were sufficiently robust to support the article's conclusions, and how potential confounds were addressed in the data analyses. Furthermore, only 31.06% of the participants in the study had RT-PCR tests confirming a COVID-19 diagnosis, although in the article all were reported as patients with COVID-19.

Also the study of D'Amato and colleagues [9] presents methodological flaws. It is not possible to understand from the text whether patients were enrolled on the basis of specific characteristics (the authors referred generically to onset of symptoms), what their age was, especially that of subjects with the worst clinical course, and whether a control group treated with standard methods was included. Furthermore, the sample size was not calculated in advance and a statistical analysis of the results was completely missing.

3.1. Conceptual flaws related to the use of the drugs chosen

Regardless of these methodological weaknesses and, maybe, possible ethical problems, there are conceptual questions about the choice of drugs and their use in these study.

3.2. Hydroxychloroquine

Currently, no direct supporting data on the effective role of chloroquine and hydroxychloroquine in the treatment for COVID-19 exist [12]. The SOLIDARITY trial launched by the World Health Organization has been unable to document an effect on overall mortality, initiation of ventilation, and duration of hospital stay in hospitalized patients [13].

A recent systematic review and meta-analysis indicated, with a moderate level of certainty, that hydroxychloroquine monotherapy lacks efficacy in reducing short-term mortality in hospitalized patients with COVID-19 or in reducing risk of hospitalization in outpatients with COVID-19 [14]. It was also found that the use of hydroxychloroquine in combination with azithromycin is probably associated with increased short-term mortality among hospitalized COVID-19 patients.

A Cochrane systematic review reached the same conclusion and stated that no further trials of hydroxychloroquine or chloroquine for treatment should be carried out [15].

Although it cannot be excluded entirely that the drug is effective in protecting people from infection [14], the results of these two large meta-analyses make it less likely.

3.3. Vitamin D

There is evidence that a low vitamin D status may partly account for adverse clinical outcomes and mortality in hospitalized patients with COVID-19. A baseline 25-hydroxyvitamin D (25(OH)D) threshold falling between 8 and 12 ng/mL might predict poor clinical outcomes in hospitalized patients with COVID-19 [16]. Nevertheless, sufficient evidence to support vitamin D supplementation with the aim of preventing or treating COVID-19 is still lacking [17].

Basically, the real efficacy of the vitamin D supplementation for prevention of, or as an adjuvant treatment for COVID-19 remains to be determined, pending results of well-designed experimental studies [18]. In any case, independent associations between low vitamin D and COVID-19 morbidity and mortality need to be established first.

A plausible doubt about the efficacy of vitamin D supplementation in subjects that do not suffer from a vitamin D deficiency derives from the analysis of data from the Australian D-Health Trial [19]. This analysis found that monthly bolus doses of 60,000 IU of vitamin D do not reduce the overall risk of acute respiratory tract infection, but may slightly reduce the duration of symptoms in the general population. These results suggest that routine vitamin D supplementation in a population that is largely full of vitamin D is unlikely to have a clinically relevant effect on acute respiratory tract infections.

When prescribing vitamin D supplementation to a SARS-CoV-2 positive patient, it must always be kept in mind that less than a third of asymptomatic subjects have a vitamin D deficiency [20]. All this suggests that total serum 25(OH)D levels should always be measured before starting the vitamin D supplementation, even in subjects that receive an outpatient treatment. Only those with low concentrations should be treated with sufficient vitamin D to achieve and maintain 25 (OH)D concentration to where a reasonable benefit would occur [21].

3.4. Oral corticosteroids

In accordance with the results of the RECOVERY trial, oral corticosteroids do not improve outcomes, and may caused harm among patients who do not receive supplemental oxygen [22]. Thus, they are not recommended for the treatment of mild or moderate COVID-19. This finding is confirmed by the results of two meta-analyses, which have showed that corticosteroids could lead to higher mortality, longer length of hospital stay, a higher rate of bacterial infection and hypokalaemia [23], and delayed virus clearing [24]. Furthermore, a nationwide, prospective, multicentre, observational, cohort study in critically ill adult patients with COVID-19 admitted into Intensive Care Units in Spain has documented that early use of corticosteroids was not as effective in women, in those with lower risk of death (younger patients with good oxygenation and less inflammation) and even in those with greater risk or severity (cancer, diabetics, D-Dimer > 1500 ng/mL, APACHE score > 14) [24]. These findings suggest that patient characteristics should be assessed before prescribing corticosteroids.

Corticosteroids limit the production of and damaging effects of cytokines, but will also inhibit the protective function of T cells and block B cells from making antibodies, potentially leading to increased plasma viral load that will persist after a patient survives SARS-CoV-2 [25]. Moreover, oral corticosteroids block macrophages from clearing secondary infections [26]. Hence it is vital to avoid corticosteroids in the initial, stable, mild-to-moderate patients with COVID-19 infections [26]. A subgroup analysis conducted in the RECOVERY study suggests that the initiation of therapy 7 or more days after the onset of symptoms may be more advantageous than treatment started within 7 days of the onset of

clinical manifestations [22]. This result is consistent with the hypothesis that corticosteroids fully exert their anti-inflammatory power at the end of the viral "replicative" phase, that is, during the "inflammatory" phase of the viral infection.

3.5. Azithromycin

The suggestion of adding azithromycin for its anti-inflammatory properties [9,27] probably stems from the observation that the use of macrolides in influenza-induced pneumonia has been associated with a faster reduction of inflammatory cytokines [28]. However it cannot be derived directly from SARS-CoV-2 infections because there is currently no evidence in a clinical setting to support the efficacy of azithromycin treatment in COVID-19 infection, as completed trials are methodologically flawed and underpowered [29].

The COALITION II trial documented that addition of azithromycin to standard of care treatment was not superior to standard of care alone in improving the clinical status in patients with severe COVID-19 [30]. Furthermore, the UK-wide Platform Randomised trial of INterventions against COVID-19 In older people (PRINCIPLE) trial, performed to test if azithromycin could help people with early stage COVID-19 to recover more quickly at home, or prevent the need for hospital admission, found that this macrolide is not generally an effective treatment for COVID-19 [31]. After 28-days of follow-up on the randomised participants (526 eligible participants were randomised to azithromycin 500 mg once daily for 3 days within the first 14-days of onset of COVID-19 and compared with 862 participants randomised to usual care), the results showed the estimated median time to self-reported recovery for azithromycin was 0.94 days shorter compared to usual care, with a low probability of being a meaningful benefit. Also, there was no evidence that azithromycin reduced hospitalisations or deaths compared with usual care. These findings confirm what was documented by the RECOVERY study, which showed that in patients hospitalized with COVID-19, azithromycin did not provide any clinical benefit [32].

It is not surprising, therefore, that major public health organisations, drug regulatory agencies and scientific societies do not recommend the use of azithromycin as a drug to treat COVID-19 infection, unless bacterial superinfections occur [33].

3.6. Low molecular weight heparin

The thromboembolic risk of COVID patients at home is not known and current evidence is not sufficient to support the role of prophylactic heparin in reducing mortality among COVID-19 patients. The French Society of Vascular Medicine has suggested that thromboprophylaxis may be considered in COVID-19 patients who have, in addition to a significant reduction in mobility, at least one of the following risk factors: BMI >30 kg/m^2, age >70 years, active cancer, personal history of venous thromboembolism, major surgery within the last three months [34]. Furthermore, a systematic review and meta-analysis of the positive effect of prophylactic heparin seems to favour patients with moderate symptoms and a combined D-dimer > 3 μg/L, platelet count >100 × 10^9/L, and PT < 14s; regardless of comorbidity, sex or age [35].

In any case, regulatory agencies and scientific societies are speaking out against the indiscriminate use of heparin and this cannot be ignored under any circumstances. According with the US National Institutes of Health (NIH), "for nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial" [36]. The Global COVID-19 Thrombosis Collaborative Group addresses non-hospitalized patients with COVID-19 and recommends consideration for anticoagulant prophylaxis for those with limited mobility, history of venous thromboembolism or active malignancy [37]. The Italian Medicines Agency (AIFA) recommends low molecular weight heparins in the initial phase of the disease only in presence of

pneumonia and hypomobility of the bedridden patient [38]. In this phase, low molecular weight heparins shall be used at a prophylactic dose in order to prevent venous thromboembolism, according to allowed indications.

4. Discussion

There is a critical and urgent need to manage COVID-19 with effective and safe drugs in order to cure symptomatic patients, but also to decrease the duration of virus carriage and thus limit transmission in the community and decrease the number of patients hospitalized. Unfortunately, there is currently no proven standard treatment available. It is true that there are many trials in progress that are evaluating new therapeutic opportunities for hospitalized patients. However, this is not the case for home treatment of patients who do not need hospitalization.

This is also the opinion of many regulatory agencies. For example, AIFA, in authorizing the use of monoclonal antibodies on February 5, 2021, stated "it may still be appropriate to offer a therapeutic option to non-hospitalized subjects who, despite having a mild/moderate disease, are at high risk of developing a severe form of COVID-19 with a consequent increase in the probability of hospitalization and/or death. *It is, in particular, a risk setting for which no standard treatment of proven efficacy is currently available*" [39]. Therefore, physicians and researchers are under pressure to identify effective treatments for COVID-19 also for subjects who are not hospitalized.

As mentioned earlier, a pandemic as serious as COVID-19 is will compel some clinicians and patients to try unproven therapies based on theory, in vitro data, animal models, clinical anecdotes, observational studies and uncontrolled trials that may later be shown to be misleading [40]. This leads to multiple small, non-controlled and non-randomised trials that would not generate the strong evidence needed to determine the relative effectiveness of potential treatments [41].

These articles are frequently published in journals of little scientific content and sometimes even in predatory journals. Regrettably, when published, these articles can lead politicians, health officers and scientists to spread often conflicting views on the effectiveness of the treatments described, ranging from miracle therapy to potentially harmful and dangerous ones. This creates great confusion among frontline physicians, who are generally so overworked that they are unable to critically follow the scientific literature, and patients who rightly do not know the differences between the various scientific journals and the processes that should lead to publication of a paper.

There is therefore a need to maintain the standards of access and acceptability of scientific studies used before the appearance of COVID-19. Indeed, a rigorous approach to evaluating studies that can have a major impact on patient health is absolutely necessary to avoid misinformation being generated.

We took a cue from the three studies that we have examined, which certainly are not the worst of the many available, as an example that allows us to highlight two points that are critical: the need for thorough peer-review processes even during this pandemic, as well as the need for medical information to be properly filtered before being disseminated by social media.

Researchers and scientific journals are ethically obligated to share only information that has been peer-reviewed. Unfortunately, the quality of the peer-review process is often poor because reviewers are a scarce resource, especially during pandemics and this can lead to an influx of low-quality publications [42]. When we define reviewers as a scarce resource, we are referring to the fact that the majority of potential reviewers, who must be experts in the field, have been under extreme pressure for many months due to their incessant and difficult clinical activities and have little time available not only to evaluate the papers, but even for a complete and unbiased professional updating.

A correct peer-review process is limited to examining only the randomised studies or trials in which, in any case, there has been a control. However, we agree that the urgency of the COVID-19 could

justify abandoning randomization [43], although without a control group, researchers would be unable to discriminate the effects caused by the investigational intervention from effects due to the natural history of the disease, patient or clinician expectations, or the effects of other interventions [44]. In particular, we strongly believe that without a randomised placebo control there is no way to know if a specific drug works better than no drug at all, although we are aware that randomization to placebo seems unethical in a pandemic. In any case, we are firmly convinced that evaluating the use of drugs in limited patient series and without a control group will be unlikely to lead to reliable and above all useable results in clinical practice.

Certainly, conventional studies are slow and demanding, and this contrasts with the absolute urgent need for effective and safe therapies. However, we cannot ignore the obligation to make every attempt to identify and approve only effective and safe therapies.

This concept is also valid when evaluating observational studies. As highlighted by the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study Registry, observational data collection requires a transparent process for selecting relevant research questions, the use of best practices in design of descriptive, predictive, and inferential studies, and innovative approaches to characterize random error in the setting of constantly updated data [45].

Another critical issue that must be always considered when designing a study is the target population [46]. It is now widely accepted that over 80% of COVID-19 cases have mild symptoms; however, 10–20% of COVID-19 cases proceed to a severe stage [47]. The identification of factors associated with the aggravation of patient symptoms from asymptomatic-mild to severe is essential for providing efficient and appropriate management to patients with COVID-19 [48].

It is therefore necessary that any paper that reports on possible therapies to be used during COVID-19 is accepted for the peer-review phase only if it reports all the necessary information that can allow duplication of the results in another study. Poorly described studies and personal opinions not supported by solid scientific evidence should not be considered for publication. If the paper is considered adequate to be peer-reviewed, editors of scientific journals need to be very careful about selecting reviewers who actually have experience with COVID-19 treatment. The publication in *Lancet* [49] and subsequent retraction of the article [50] on hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19 teaches us that even a careful analysis of papers may be insufficient to avoid misinformation. In this pandemic, journal editors need to be particularly vigilant at assessing the evidence in real time.

While it is true that the publication of poor quality papers in scientific journals produces misinformation, it is equally true that the indiscriminate dissemination of this misinformation takes place through social media and other outlets.

Undesirably, the impact at the media and citizen level deriving from the premature communication of favourable results of uncontrolled studies conducted on small case studies and in the absence of an external event evaluation committee is to receive considerable publicity as 'treatments' by the media, aided in some cases by approval as 'revolutionaries' by celebrities and high-profile politicians [51]. This is a non-negligible risk that must be avoided because it can generate inappropriate behaviours and expectations on the part of physicians and, especially, patients, and may distract us from our duty to ensure the best care for the patient.

We strongly believe that more awareness is needed on the part of readers, including physicians, in this new and rapidly changing time. Observational studies currently seem to prevail over controlled clinical trials for the reasons we have outlined.

In any case, it will always be advisable for the readers, especially if they are physicians, to ask themselves some fundamental questions about the appropriateness of the study, even if it passed the peer-review process [52]. They must take into account its design, inclusion and exclusion criteria, and outcome measures. Obviously, it is also necessary

to verify that the confounding factors have been properly controlled, the sources of bias in data have been minimized and the results and conclusions have been appropriate. But above all, they must ask themselves what the real meaning of the study is when it is introduced into clinical practice.

Ultimately, an accurate evaluation of the studies submitted to scientific journals is necessary, which entails an even greater responsibility for editors and reviewers. As it is not possible in an intellectually free world to prevent the spread of information through the media, there is a need for all those who do research to adhere to a strict ethical behaviour that prevents the spread of misinformation. The axiom of anyone interested in COVID-19 treatment must be "There can be no expectations in the absence of solid evidence."

References

[1] C. Tonne, Lessons from the COVID-19 pandemic for accelerating sustainable development, Environ. Res. 193 (2021) 110482.

[2] D.L. Weiner, V. Balasubramaniam, S.I. Shah, J.R. Javier, COVID-19 impact on research, lessons learned from COVID-19 research, implications for pediatric research, Pediatr. Res. 88 (2) (2020) 148–150.

[3] S.B. Naeem, R. Bhatti, The Covid-19 'infodemic': a new front for information professionals, Health Inf. Libr. J. 37 (3) (2020) 233–239.

[4] C.C. Lai, T.P. Shih, W.C. Ko, H.J. Tang, P.R. Hsueh, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges, Int. J. Antimicrob. Agents 55 (3) (2020) 105924.

[5] Pirro M. Covid, svolta con la terapia napoletana: «Medicinali subito e nessun decesso». Available at: https://www.ilmattino.it/primopiano/sanita/coronavirus _terapia_napoletana-5726333.html..

[6] Raoult D. Coronavirus: vers une sortie de crise ? [Video]. Available at: https://www.youtube.com/watch?v=8L6ehRif-v8..

[7] P. Gautret, J.C. Lagier, P. Parola, et al., Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, Int. J. Antimicrob. Agents 56 (1) (2020) 105949.

[8] Z. Maghbooli, M.A. Sahraian, M. Ebrahimi, et al., Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection, PloS One 15 (9) (2020), e0239799.

[9] G. D'Amato, L. Acanfora, L. Delli Paoli, M. D'Amato, Preventive home therapy for symptomatic patients affected by COVID-19 and followed by teleconsultations, Multidisc Respir Med 16 (2021) 748.

[10] F.R. Rosendaal, Review of: "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial Gautret et al 2010, Int. J. Antimicrob. Agents 56 (1) (2020) 106063, https://doi.org/10.1016/j. ijantimicag.2020.105949.

[11] PLOS ONE Editors. Expression of Concern: vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection, PloS One 15 (10) (2020), e0240965.

[12] A. Gasmi, M. Peana, S. Noor, et al., Chloroquine and hydroxychloroquine in the treatment of COVID-19: the never-ending story, Appl. Microbiol. Biotechnol. 105 (4) (2021) 1333–1343.

[13] WHO Solidarity Trial Consortium, Repurposed antiviral drugs for covid-19 - interim WHO solidarity trial results, N. Engl. J. Med. 384 (6) (2021) 497–511.

[14] Z. Kashour, M. Riaz, M.A. Garbati, et al., Efficacy of chloroquine or hydroxy-chloroquine in COVID-19 patients: a systematic review and meta-analysis, J. Antimicrob. Chemother. 76 (1) (2021) 30–42.

[15] B. Singh, H. Ryan, T. Kredo, et al., Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19, Cochrane Database Syst. Rev. 2 (2021) CD013587.

[16] M. Infante, A. Buoso, M. Pieri, et al., Low Vitamin D status at admission as a risk factor for poor survival in hospitalized patients with COVID-19: an Italian retrospective study, J. Am. Coll. Nutr. (2021), https://doi.org/10.1080/ 07315724.2021.1877580 (Epub ahead of print).

[17] The Lancet Diabetes Endocrinology, Vitamin D and COVID-19: why the controversy? Lancet Diabetes Endocrinol 9 (2) (2021) 53.

[18] M. Chakhtoura, N. Napoli, G. El Hajj Fuleihan, Commentary: myths and facts on vitamin D amidst the COVID-19 pandemic, Metabolism 109 (2020) 154276.

[19] H. Pham, M. Waterhouse, C. Baxter, et al., The effect of vitamin D supplementation on acute respiratory tract infection in older Australian adults: an analysis of data from the D-Health Trial, Lancet Diabetes Endocrinol 9 (2) (2021) 69–81.

[20] A. Jain, R. Chaurasia, N.S. Sengar, et al., Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers, Sci. Rep. 10 (1) (2020) 20191.

[21] P. Pludowski, M.F. Holick, W.B. Grant, et al., Vitamin D supplementation guidelines, J. Steroid Biochem. Mol. Biol. 175 (2018) 125–135.

[22] P. Horby, W.S. Lim, J.R. Emberson, et al., Dexamethasone in hospitalized patients with covid-19 - preliminary report, N. Engl. J. Med. (2020), https://doi.org/ 10.1056/NEJMoa2021436.

[23] Z. Yang, J. Liu, Y. Zhou, et al., The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis, J. Infect. 81 (1) (2020) e13–e20.

[24] H. Li, C. Chen, F. Hu, et al., Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis, Leukemia 34 (6) (2020) 1503–1511.

[25] P. Monedero, A. Gea, P. Castro, et al., Early corticosteroids are associated with lower mortality in critically ill patients with COVID-19: a cohort study, Crit. Care 25 (1) (2021) 2.

[26] T.C. Theoharides, P. Conti, Dexamethasone for COVID-19? Not so fast, J. Biol. Regul. Homeost. Agents 34 (3) (2020) 1241–1243.

[27] F. Suter, N. Perico, M. Cortinovis, G. Remuzzi, A recurrent question from a primary care physician: how should I treat my COVID-19 patients at home? An update, Clin Med Invest (2020), https://doi.org/10.15761/CMI.1000218.

[28] N. Lee, C.K. Wong, M.C.W. Chan, et al., Anti-inflammatory effects of adjunctive macrolide treatment in adults hospitalized with influenza: a randomized controlled trial, Antivir. Res. 144 (2017) 48–56.

[29] J. Sultana, S. Crisafulli, F. Gabbay, et al., Challenges for drug repurposing in the COVID-19 pandemic era, Front. Pharmacol. 11 (2020) 588654.

[30] R.H.M. Furtado, O. Berwanger, H.A. Fonseca, et al., Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial, Lancet 396 (10256) (2020) 959–967.

[31] Anonymous. PRINCIPLE trial finds antibiotics azithromycin and doxycycline not generally effective treatments for COVID-19. Available at: https://www.ox.ac.uk/news/2021-01-25-principle-trial-finds-antibiotics-azithromycin-and-doxycycline-not-generally..

[32] P.W. Horby, E. Roddick A Spata, et al., Azithromycin in hospitalised patients with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial, Available at: https://www.medrxiv.org/content/10.1101/2020.12.10.20245944v1.

[33] J. Sultana, P.M. Cutroneo, S. Crisafulli, et al., Azithromycin in COVID-19 patients: pharmacological mechanism, clinical evidence and prescribing guidelines, Drug Saf. 43 (8) (2020) 691–698.

[34] L. Khider, S. Soudet, D. Laneelle, et al., Proposal of the French Society of Vascular Medicine for the prevention, diagnosis and treatment of venous thromboembolic disease in outpatients with COVID-19, J Med Vasc 45 (4) (2020) 210–213.

[35] M. Abdel-Maboud, A. Menshawy, A. Elgebaly, et al., Should we consider heparin prophylaxis in COVID-19 patients? a systematic review and meta-analysis, J. Thromb. Thrombolysis (2020), https://doi.org/10.1007/s11239-020-02253-x.

[36] National Institutes of Health COVID-19 Treatment Guidelines. Antithrombotic therapy in patients with COVID-19. Last Updated: December 17, 2020. Available at: https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy/..

[37] B. Bikdeli, M.V. Madhavan, D. Jimenez, et al., Global COVID-19 thrombosis collaborative group, endorsed by the ISTH, NATF, ESVM, and the IUA, supported by the ESC working group on pulmonary circulation and right ventricular function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review, J. Am. Coll. Cardiol. 75 (23) (2020) 2950–2973.

[38] AIFA. Italian Medicines Agency. Low molecular weight heparins in the treatment of adult patients with COVID-19. Update: 24 November 2020. Available at: https://www.aifa.gov.it/documents/20142/1267737/Low-molecular-weight-heparins_EN_24.11.2020.pdf/fc92d837-e27a-17af-18db-9a8635fb19d5..

[39] AIFA. Italian Medicines Agency. AIFA pubblica parere CTS su anticorpi monoclonali. Available at: https://www.aifa.gov.it/-/aifa-pubblica-parere-cts-su-anticorpi-monoclonali..

[40] I.A. Scott, COVID-19 pandemic and the tension between the need to act and the need to know, Intern. Med. J. 50 (8) (2020) 904–909.

[41] Rion Logean S. The science, progress and high stakes of COVID-19 drug developments. Available at: https://www.swissre.com/reinsurance/life-and-health/l-h-risk-trends/science-progress-high-stakes-covid-19-drug-developments.html..

[42] H. Hashem, M. Abufaraj, A. Tbakhi, I. Sultan, Obstacles and considerations related to clinical trial research during the COVID-19 pandemic, Front. Med. 7 (2020) 598038.

[43] R.M. Califf, L.H. Curtis, R.A. Harrington, A.F. Hernandez, E.D. Peterson, Generating evidence for therapeutic effects: the need for well-conducted randomized trials, J. Clin. Invest. 131 (2) (2021) e146391.

[44] S.R. Evans, Fundamentals of clinical trial design, J Exp Stroke Transl Med 3 (1) (2010) 19–27.

[45] A.J. Walkey, R.C. Sheldrick, R. Kashyap, V.K. Kumar, S. Boman, S. Bolesta, F. G. Zampieri, V. Bansal, M.O. Harhay, O. Gajic, Guiding principles for the conduct of observational critical care research for coronavirus disease 2019 pandemics and beyond: the society of critical care medicine Discovery viral infection and respiratory illness universal study registry, Crit. Care Med. 48 (11) (2020) e1038–e1044.

[46] Y. Wang, Y. Wang, Y. Chen, Q. Qin, Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures, J. Med. Virol. 92 (6) (2020) 568–576.

[47] M.H. Gail, D.G. Altman, S.M. Cadarette, G. Collins, S.J. Evans, P. Sekula, E. Williamson, M. Woodward, Design choices for observational studies of the effect of exposure on disease incidence, BMJ Open 9 (12) (2019), e031031.

[48] M.C. Chang, Y.K. Park, B.O. Kim, D. Park, Risk factors for disease progression in COVID-19 patients, BMC Infect. Dis. 20 (1) (2020) 445.

[49] The Lancet Editors. Expression of concern: hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis, Lancet 395 (10240) (2020), e102.

[50] M.R. Mehra, F. Ruschitzka, A.N. Patel, Retraction - hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis, Lancet 395 (10240) (2020) 1820.

[51] M. Liu, T.L. Caputi, M. Dredze, A.S. Kesselheim, J.W. Ayers, Internet searches for unproven COVID-19 therapies in the United States, JAMA Intern Med 180 (8) (2020) 1116–1118.

[52] K.M. Shields, N.A. DiPietro, K.L. Kier, Principles of drug literature evaluation for observational study designs, Pharmacotherapy 31 (2) (2011) 115–127.

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