Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dkaa564

Evolution of practices regarding COVID-19 treatment in France during the first wave: results from three cross-sectional surveys (March to June 2020)

S. Rolland [1,2]*, D. Lebeaux[3,4], P. Tattevin[5], O. Launay[1,6] and L. B. Luong Nguyen[1]

[1]INSERM CIC 1417 Cochin Pasteur, AP-HP, Hôpital Cochin, 75014 Paris, France; [2]Infectious Diseases Department, Cavale Blanche University Hospital, 29200 Brest, France; [3]Université de Paris, F-75006 Paris, France; [4]Service de Microbiologie, Unité Mobile d'Infectiologie, AP-HP, Hôpital Européen Georges Pompidou, 75015 Paris, France; [5]Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, 35000 Rennes, France; [6]Université de Paris, Faculté de médecine Paris Descartes, INSERM CIC 1417, F-CRIN, I REIVAC, 75014 Paris, France

*Corresponding author. E-mail: simon.g.rolland@gmail.com

Sir,

At the beginning of the first epidemic wave of COVID-19 in France, physicians had to manage severely ill patients in the absence of any treatment with documented clinical efficacy. Several repurposed drugs have been used for COVID-19 treatment,[1] such as antivirals (remdesivir, lopinavir), immunomodulatory drugs (corticosteroids, tocilizumab, anakinra) or hydroxychloroquine, with poor results for most of them as of today.[2] Throughout the epidemic, their use has been a subject of lively debate in France by the scientific community and in the media. Physicians also rapidly had the possibility to include patients in therapeutic trials. In this context of an initial lack of validated treatment, we aimed to describe physicians' practices during this first epidemic wave of COVID-19 in France.

We performed three online surveys among members of the French society of infectious diseases (Société de Pathologie Infectieuse de Langue Française; SPILF) on the 22 March, the 23 April and the 09 June. Surveys were broadcast to the 700 subscribers of the SPILF mailing list. The questionnaires aimed to collect characteristics of the physicians' centres (hospital, service, and region), participation in clinical trials, and drugs used for COVID-19 treatment. The questionnaire mostly used multiple-choice questions. All data were reported as count and percentages in a univariate analysis. Fisher's exact test was used to compare proportions when appropriate.

A total of 144 complete questionnaires were collected from 115 physicians: 60 in March, 54 in April and 30 in June. Five physicians answered all three surveys. All regions of metropolitan France were represented. Among the 115 physicians, 54 (47%) were working in a university hospital, and 51 (44%) in a public hospital. Seventy-seven (67%) worked in infectious diseases departments, and 9 (8%) in intensive care units. The characteristics of respondents did not change across time (Table S1, available as Supplementary data at *JAC* Online).

Participation in trials was reported by 19/60 clinicians (32%) in March, compared with 40/54 clinicians (74%) in April. Participation rate in clinical studies was lower in June (17/30, 57%). The clinical studies were all French, except for one (DisCoVeRy, NCT04315948). Among physicians involved in clinical studies, hospital type differed significantly during the March and April surveys. The proportion working in a non-University hospital increased from 16% (3/19) in March, to 37% (15/40) in April and 53% (9/17) in June (Table S2).

Specific treatment for COVID-19 was reported for 46/60 (77%) questionnaires in March, 35/54 (65%) in April, and 27/30 (90%) in June. From March to June, we observed a shift in drug preferences over time, with a decrease of hydroxychloroquine prescription, whereas the use of immunomodulating drugs as a whole (corticosteroids, tocilizumab and anakinra) increased. There was also a rise in the prescription of remdesivir. Surprisingly, lopinavir/ritonavir prescription remained stable (Figure 1). When analysing each survey separately, prescription of specific treatment and choice of drugs did not differ according to clinicians' region, type of hospital, hospitalization unit, or participation in a clinical study.

Early on, physicians were hard-pressed to identify any molecules that might be beneficial to patients. They had to consider the prescription of repurposed drugs, such as hydroxychloroquine or lopinavir/ritonavir, as shown by the results of the March and April surveys. As our study went on, results of randomized controlled trials were published. The preliminary results of remdesivir trial published by Beigel *et al.*,[3] showed a benefit of remdesivir in reducing time to recovery compared with placebo. Although limited, these data offered an alternative to hydroxychloroquine, which was banned as a COVID-19 treatment after several studies failed to show benefit for patients,[4,5] and was confirmed later; [6] our June survey captured this prescription shift. By the end of our study, the preliminary report of the RECOVERY trial had been communicated,[7] with a robust outcome showing a reduced mortality for critically ill patients receiving dexamethasone, a finding that has been confirmed over time.[8,9] Several weeks before this major breakthrough, physicians were already considering using corticosteroids because of pathophysiological data describing an inappropriate immune response in severe COVID-19, resulting in a so-called 'cytokine storm'.[10] In accordance, we observed a continuous rise in the use of various immunomodulatory drugs, and corticosteroids ended up as the favoured drug in June.

Despite of its low participation rate caused by the overwhelming workload on physicians, this study still provides new insights in the particular context of an emerging disease, witnessing the pace at which clinicians' practices evolved. Interestingly, practices did not seem to differ according to the characteristics of the centres where clinicians worked, or their access to clinical studies.

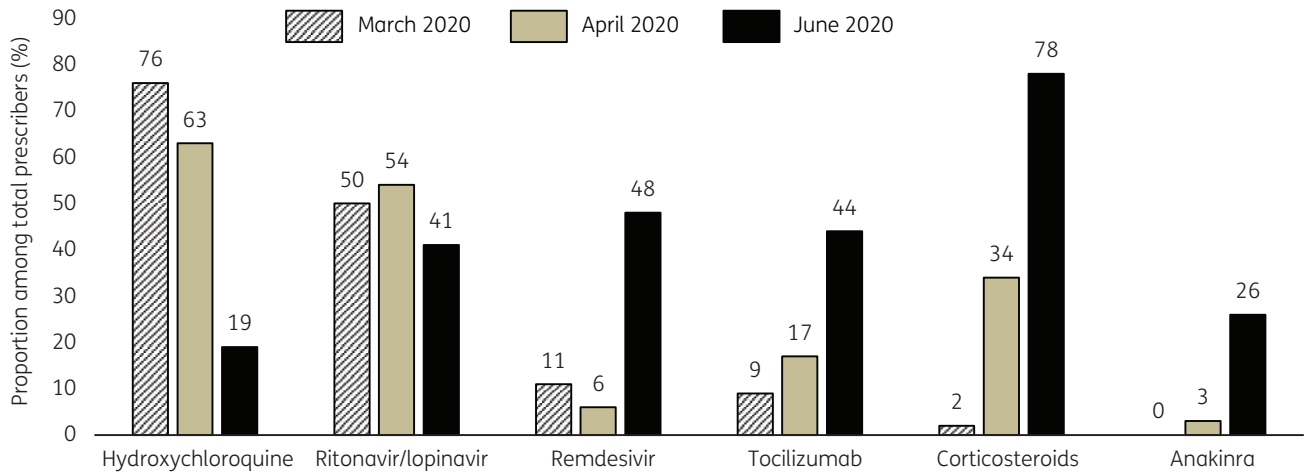

Figure 1. Evolution of treatment practices for COVID-19 in France, March to June 2020. Proportion of reported prescription for hydroxychloroquine, ritonavir/lopinavir, remdesivir, tocilizumab, corticosteroids and anakinra are represented among total prescribers according to the month of response. Each column represents the percentage of response among prescribers, the value is reported on the top of the column. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

This longitudinal survey also captured the early impact of clinical studies, though perhaps a more coordinated effort with better access for all physicians might have brought more significant results.

Acknowledgements

Results were presented during the 21st National Congress of Infectious Disease, in Poitiers, France, 10 September 2020 (oral communication, ID COL7-3). Results were presented during the ESCMID Conference on Coronavirus Disease in September 2020 (e-Poster, abstract ID 00372).

Funding

This study was conducted as part of our routine work.

Transparency declarations

None to declare. All data associated with this study is available in the main text or the Supplementary data.

Author contributions

Conception and design of the study: O.L., P.T., D.L., L.B.L.N. Acquisition of data: O.L., P.T., D.L., L.B.L.N., S.R. Analysis and interpretation of data: O.L., L.B.L.N., S.R. Drafting article: S.R. Revising article: L.B.L.N., O.L., P.T., D.L. All authors reviewed and approved the final version of the manuscript.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online.

References

1 Li G, Clercq ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov* 2020; **19**: 149–50.

2 WHO Solidarity Trial Consortium, Pan H, Peto R *et al.* Repurposed antiviral drugs for COVID-19 - Interim WHO Solidarity trial results. *N Engl J Med* 2020; doi:10.1056/NEJMoa2023184.

3 Beigel JH, Tomashek KM, Dodd LE *et al.* Remdesivir for the treatment of COVID-19—final report. *N Engl J Med* 2020; **383**: 1813–26.

4 HCSP. Avis du haut conseil de la santé publique relatif à l'utilisation de l'hydroxychloroquine dans la COVID-19. 2020. https://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspa20200524_covidutilidelhydro.pdf.

5 Lane JCE, Weaver J, Kostka K *et al.* Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study. *Lancet Rheumatol* 2020; **2**: e698–711.

6 Fiolet T, Guihur A, Rebeaud M *et al.* Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis. *Clin Microbiol Infect* 2021; **27**: 19–27.

7 University of Oxford. RECOVERY Trial. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. 2020. https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf.

8 WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S *et al.* Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020; **324**: 1330–41.

9 RECOVERY Collaborative Group, Horby P, Lim WS *et al.* Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med* 2020; doi:10.1056/NEJMoa2021436.

10 Azkur AK, Akdis M, Azkur D *et al.* Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* 2020; **75**: 1564–81.