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Hydroxychloroquine, Interleukin-6 Receptor Antagonists and Corticoid Treatments of Acute COVID-19 Infection: Psychiatric Symptoms and Mental Disorders 4 Months Later

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Objective: Psychiatric symptoms and mental disorders are common after Coronavirus Disease-19 (COVID-19). Some drugs used to treat acute COVID-19 have psychiatric side effects. We assessed the psychiatric symptoms and mental disorders of patients treated for acute COVID-19 with hydroxychloroquine (HCQ), interleukin-6 receptor antagonists (anti-IL-6), and corticoids (CTC).
Methods: We evaluated 177 patients in a day hospital 4 months after acute infection.
Results: In a multivariate analysis, HCQ was associated with significant anxiety symptoms (odds ratio [OR] = 5.9, 95% confidence interval [95% CI] = 1.8−20.0, $p = 0.003$) and mental disorders (OR = 4.1, 95% CI = 1.2−13.9, $p = 0.02$). In a bivariate analysis with propensity matched cohorts, HCQ was associated with significant anxiety symptoms (9 patients [50.0%] with significant symptoms in the HCQ group versus 15 [20.1%] in the control group, OR = 3.8, 95% CI = 1.3−11.3, $p = 0.01$). Anti-IL-6 and CTC were not associated with significant psychiatric symptoms or mental disorders.
Conclusion: We recommend monitoring psychiatric symptoms, especially anxiety, in patients treated with HCQ during COVID-19 infection. Further studies with larger samples and prospective assessments are needed to confirm our results.

KEY WORDS: Major depressive disorder; Anxiety; COVID-19.

INTRODUCTION

Psychiatric symptoms—including insomnia, anxiety, or depressive symptoms [1,2]—and mental disorders—such as major depressive episodes (MDE) and anxiety disorders [3,4]— are frequently reported in the months following an acute Coronavirus Disease-19 (COVID-19) episode. To date, little is known about the influence of COVID-19 treatments on psychiatric outcomes. Some drugs prescribed during acute phase COVID-19 are known to have psychiatric side effects. Hydroxychloroquine (HCQ) was broadly used [5,6] during the first months of the pandemic before scientific evidence of its inefficacy was established [7]. HCQ is an antimalarial drug and an immunomodulatory treatment for systemic lupus erythematosus. Psychiatric side effects (particularly MDE) have been described [8,9]. Corticoids, anti-inflammatory drugs used in severe COVID-19 [10], are known to have a poor psychiatric tolerance and to induce depressive or manic symptoms [11]. Interleukin-6 receptor antagonists (anti-IL-6), monoclonal antibodies that inhibit the interleukin-6 (IL-6) signaling pathway, have been used in cases of hospitalized COVID-19

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and are associated with decreased depressive symptoms in inflammatory diseases [12]. Hence, our aim was to assess the association between drugs prescribed for acute COVID-19 infection and psychiatric outcomes 4 months after acute COVID-19.

METHODS

The COMEBAC (Consultation Multi-Expertise de Bicêtre Après COVID-19) [2] cohort prospectively included adult patients admitted to Bicêtre hospital (Assistance Publique-Hopitaux de Paris, France) for COVID-19 during the first wave of the pandemic in France (from March 1 to May 29, 2020) and who survived four months (median time 120 days, interquartile range 34 days) after hospital discharge. The COMEBAC study was designed to assess the lingering symptoms after COVID-19 in patients hospitalized at Bicêtre hospital for the COVID-19, after the first wave of COVID-19 in France, which last from march 2020 to may 2022. Study design and day hospital were planned in June 2020, and we evaluated patients from July to September 2020. 478 patients were contacted by telephone, 294 (61.5%) were invited to the day hospital and, among them, 177 (37.0%) were evaluated. The main inclusion criteria were: age $\geq$ 18 years old, hospitalized for more than 24h primarily in relation to COVID-19, with a SARS-CoV-2 infection diagnosed by reverse transcriptase polymerase chain reaction and/or by a typical lung computed tomography scan associated with clinical features, with at least one post-acute COVID-19 sequelae or having been hospitalized in an intensive care unit (ICU) during hospital stay. During the day hospital, patients responded to the following self-assessment questionnaires focused on psychiatric symptoms: the Insomnia Severity Index (ISI) [13] for insomnia; the Hospital Anxiety and Depression scale-anxiety subscale (HAD-A) [14] for anxiety symptoms; the Beck Depression Inventory-13 items (BDI-13) [15] for depressive symptoms; the Post-Traumatic Stress Disorders (PTSD) Check-List for Diagnostic and Statistical Manual of Mental Disorders- 5th version (DSM-5) [16] for post-traumatic symptoms. Significant psychiatric symptoms were defined as: a ISI score $>$ 14 for insomnia [13]; a HAD-A score $>$ 7 for anxiety [14]; a BDI score $>$ 7 for depression [15]; a PCL-5 (post traumatic disorder checklist for DSM-5) score $>$ 30 for PTSD [16]. Mental disorders were evaluated through systematic interviews (Mini International Neuropsychiatric Interview for DSM-5 [17]) with trained psychiatrists. The COMEBAC cohort has been recently described [2]. Patients provided written informed consent. The Ethics Committee of the French Intensive Care Society (CE20-56) approved the study.

Several drugs prescribed to treat the acute COVID-19 infection were extracted from medical records: HCQ (n = 18, mean dose [md] = 427.3 mg/d, mean treatment duration [td] = 6.1 days); corticoids (CTC) (n = 7, md = 80.6 mg, td = 16.0 days); anti-IL-6 (sarilumab: n = 26, md = 800 mg twice times; tocilizumab: n = 1, dose = 600 mg). Seven patients received a combination of two drugs (5 HCQ and anti IL-6, 1 HCQ and CTC, 1 CTC and Anti IL-6). 132 patients did not receive any of these treatments.

Patients treated with these drugs were compared to those who did not receive any treatment (control group) for baseline medical characteristics (age, sex, body mass index, history of psychiatric disorders, asthma, smoking, antidepressant drugs, maximal plasmatic C-reactive protein and creatininemia during acute COVID-19, intubation, and intensive care unit [ICU] stay during hospitalization) and for the presence of significant psychiatric symptoms and psychiatric disorders 4 months after acute COVID-19 infection (all mental disorders, MDE, and anxiety disorders). Bivariate analyses were performed to compare the control group to patients receiving treatment. For each treatment, multivariate analyses were performed adjusting for age, sex, history of mental disorders, and invasive ventilation or ICU stay to account for COVID-19 severity. Propensity score matched cohorts were built with age, sex, history of mental disorder and ICU stay as a-priori variables, and any variables with a significant trend ($p <$ 0.2) in bivariate analyses [18]. Psychiatric symptoms and mental disorders were compared in each matched cohort with chi-square tests and Fisher Exact tests for non-parametric variables. Statistical analyses were performed using R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The mean patient age was 57.5 years (standard deviation [SD] = 13.2). Sixty-eight patients (38.4%) were female. During acute COVID-19 infection, 97 patients (54.8%) were admitted to the ICU and 51 (28.8%) required invasive ventilation. Four months after discharge, 36 (20.3%) pa-

tients had at least one mental disorder, including 24 (13.6%) with a MDE, 20 (11.3%) with an anxiety disorder, 7 (4.0%) with a PTSD and 3 (1.7%) with an obsessive compulsive disorder. In bivariate analyses, no difference between patients and controls was found (Table 1). In the multivariate analysis adjusted for age, sex, history of mental disorders, and ICU stay, HCQ was associated with significant anxiety symptoms (odds ratio [OR] = 5.9, 95% confidence interval [95% CI] = 1.8−20.0, p = 0.003), mental disorders (OR = 4.1, 95% CI = 1.2−13.9, p = 0.02), and MDE (OR = 5.0, 95% CI = 1.3−17.9, p = 0.01). In the multivariate analysis adjusted for age, sex, history of mental disorders, and invasive ventilation, HCQ was associated with significant anxiety symptoms (OR = 5.6, 95% CI = 1.8−18.7, p = 0.004), mental disorders (OR = 3.7, 95% CI = 1.1−12.2, p = 0.03), and MDE (OR = 4.6, 95% CI = 1.2−16.3, p = 0.02). HCQ was still associated with those outcomes when prescription of another treatment (CTC or anti-IL-6) was integrated as a covariate in the logistic regression model. Anti-IL-6 and CTC were not associated with significant psychiatric symptoms or mental disorders.

In bivariate analyses within propensity score matched cohorts, HCQ was associated with significant anxiety symptoms (9 patients [50.0%] with significant symptoms in the HCQ group versus 15 [20.1%] in the control group, OR = 3.8, 95% CI = 1.3−11.3, p = 0.01), while anti-IL-6 was associated with significant depressive symptoms (p = 0.04) (Supplementary Table 1; available online). CTC was not associated with psychiatric symptoms or mental disorders.

Table 1. Baseline characteristics, significant psychiatric symptoms and mental disorders 4 months after discharge in patients treated by three drug treatment and controls

	Controls (n = 132)	HCQ (n = 18)	Anti-IL-6 (n = 27)	CTC (n = 7)
Baseline characteristics				
Age (yr)	57.0 ± 13.9	57.55 ± 11.5	61.6 ± 10.5	52.7 ± 8.5
Female	57 (43.2)	4 (22.2)	9 (33.3)	1 (14.3)
BMI (kg/m^2)	28.0 ± 7.8	29.7 ± 5.4	27.56 ± 7.4	29.6 ± 6.8
History of psychiatric disorders	11 (8.3)	1 (5.6)	6 (22.2)[a]	1 (14.3)
High blood pressure	56 (42.4)	7 (38.9)	15 (55.6)	1 (14.3)
Type 2 diabete	41 (31.1)	5 (27.8)	7 (25.9)	2 (28.6)
COPD	5 (3.8)	0	0	0
Asthma	22 (16.7)	5 (27.8)	3 (11.1)	0
Smoking	10 (7.6)	1 (5.6)	5 (18.5)	0
Antidepressant drugs	6 (4.5)	1 (5.6)	4 (14.8)[a]	0
Plasmatic CRP	141.6 ± 108.1	113.9 ± 87.4	170.4 ± 102.7	284.7 ± 157.4*
Maximal creatininemia	120.5 ± 154.8	160.1 ± 178.3	179.2 ± 219.0[a]	124.9 ± 114.2
Intubation	32 (24.2)	7 (38.9)	12 (44.4)[a]	5 (71.4)[a]
ICU stay	63 (47.7)	13 (72.2)	20 (74.1)	7 (100.0)
Significant psychiatric symptoms 4 months after the acute COVID-19 infection				
Insomnia (ISI > 14)	31 (23.5)	4 (22.2)	6 (22.2)	0
Anxiety (HAD > 7)	38 (28.8)	9 (50.0)[b]	10 (37.0)	1 (14.3)
Depression (BDI > 7)	24 (18.2)	4 (22.2)	9 (33.3)	0
Mental disorders 4 months after the acute COVID-19 infection				
All mental disorders	26 (19.7)	6 (33.3)[b]	8 (29.6)	1 (14.3)
Major depressive disorders	16 (12.1)	5 (27.8)[b]	6 (22.2)	1 (14.3)
Anxiety disorders	15 (11.4)	2 (11.1)	4 (14.8)	0

Values are presented as mean ± standard deviation or number (%).
HCQ, hydroxychloroquine; Anti-IL-6, interleukin-6 receptor antagonists; CTC, corticotherapy; BMI, body mass index COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; ISI, Insomnia Severity Index; HAD, Hospital Anxiety and Depression; BDI, Beck Depression Inventory.
[a]Variables with $p < 0.2$ used to build propensity matched cohorts (in addition to age, sex, history of mental disorders and ICU stay). [b]Variables statistically significant in multivariate analysis.
Seven patients received a combination of two drugs (5 HCQ and anti-IL-6, 1 HCQ and CTC, 1 CTC and anti-IL-6).
*Statistically significant ($p < 0.05$) differences with controls.

DISCUSSION

HCQ prescribed during acute COVID-19 infection was associated with psychiatric outcomes—especially anxiety symptoms—4 months after infection. A poor psychiatric tolerance to HCQ was reported in a global database of individual case safety reports [19]. The physiological mechanisms through which HCQ induces psychiatric symptoms remain unclear, but its immunomodulatory effect and lysosomal inhibition are the two main hypotheses [20]. Its long half-life [20] could explain the long-lasting anxiety symptoms 4 months after acute COVID-19 infection. This result is in line with previous reports about poor psychiatric tolerance to HCQ [8,9,19]. Anti-IL-6, which are associated with decreased depressive symptoms [12] in inflammatory diseases, were not associated with a reduced prevalence of psychiatric symptoms or mental disorders in our cohort. Between propensity score matched cohorts, significant depressive symptoms were higher in the anti-IL-6 group than in the matched cohort. This result, close to the significance threshold, should be replicated in a larger sample. Corticoids were not associated with significant psychiatric symptoms or mental disorders. Patients treated with HCQ may present with more psychiatric symptoms and disorders due to the severity of the initial disease. To take this potential bias into account, separate multivariate analyses for ICU stay and invasive ventilation were performed. Furthermore, no association was found between the severity of acute COVID-19 infection and mental disorders 4 months after COVID infection in a recent study [21]. This study has limitations. First, it was conducted in a relatively small sample, and the analysis of socioeconomic factors was limited. Second, it was a retrospective naturalist study and not a prospective randomized controlled trial. Propensity score matching is a method that allows for the comparison of a control group and a pseudo-randomized (i.e., matched) cohort to minimize bias [18]. Third, even if history of a psychiatric disorder was reported in medical records, psychiatric symptoms could have appeared before COVID-19 infection. Fourth, we do not have any information regarding patient vaccination status. Fifth, after COVID-19, it is known that psychiatric symptoms such as anxiety, depression, insomnia, and suicidal ideation can occur due to various factors. Larger and prospective studies are needed to confirm the long-term effect(s) of acute COVID treatment on mental health.

We report anxiety symptoms 4 months after HCQ treatment for acute COVID. Further studies with larger samples and prospective assessments are needed to confirm this safety concern. We recommend monitoring psychiatric outcomes, especially anxiety, in patients treated with HCQ during COVID-19 infection.

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■ Conflicts of Interest

Dr Montani reported personal fees from Actelion, GSK, Pfizer, MSD, Chiesi, Boehringer, and Incyte Biosciences France; grants from Bayer and MSD; and nonfinancial support from Acceleron, outside the submitted work. Dr Monnet reported personal fees from Getinge Pulsion Medical and Baxter outside the submitted work. Dr Becquemont reported grants from Sanofi Genzyme for a presentation concerning Gaucher disease, and pharmacogenetics and drug interactions with Eliglustat outside the submitted work. No other disclosures were reported.

■ Author Contributions

Conceptualization: Matthieu Gasnier, Romain Colle. Data acquisition: Matthieu Gasnier, Romain Colle. Formal analysis: Matthieu Gasnier. Supervision: Romain Colle, Emmanuelle Corruble. Writing—original draft: Matthieu Gasnier. Writing—review & editing: Walid Choucha, David Montani, Nicolas Noël, Céline Verstuyft, Francois Radiguer, Xavier Monnet, Laurent Becquemont.

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