


A prospective, observational study to evaluate adverse drug reactions in patients with COVID-19 treated with remdesivir or hydroxychloroquine: a preliminary report

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ABSTRACT

Objectives Since the outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the pressure to minimise its impact on public health has led to the implementation of different therapeutic strategies, the efficacy of which for the treatment of coronavirus disease 2019 (COVID-19) was unknown at the time. Remdesivir (REM) was granted its first conditional marketing authorisation in the EU in June 2020. The European Medicines Agency (EMA) and local health authorities all across the EU have since strongly recommended the implementation of pharmacovigilance activities aimed at further evaluating the safety of this new drug. The objective of this study was to evaluate adverse drug reactions (ADRs) attributed to either REM or hydroxychloroquine (HCQ) in patients hospitalised for COVID-19 in Centro Hospitalar de Lisboa Ocidental, a Portuguese hospital centre based in Lisbon. We present the preliminary results reporting plausible adverse effects of either HCQ or REM.

Methods An observational cohort study was carried out between 16 March and 15 August 2020. Participants were divided into two cohorts: those prescribed an HCQ regimen, and those prescribed REM. Suspected ADRs were identified using an active monitoring model and reported to the Portuguese Pharmacovigilance System through its online notification tool. The ADR cumulative incidence was compared between the two cohorts.

Results The study included 149 patients, of whom 101 were treated with HCQ and the remaining 48 with REM. The baseline characteristics were similar between the two cohorts. A total of 102 ADRs were identified during the study period, with a greater incidence in the HCQ cohort compared with the REM cohort (47.5% vs 12.5%; $p < 0.001$). Causality was assessed in 81 ADRs, all of which were considered possible.

Conclusions Real-world data are crucial to further establish the safety profile for REM. HCQ is no longer recommended for the treatment of COVID-19.

INTRODUCTION

On 10 January 2020, the Chinese Centre for Disease Control and Prevention (CDC) publicly shared the gene sequence of a novel β -coronavirus, later called

severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and confirmed to have caused coronavirus disease 2019 (COVID-19).^{1,2}

The WHO declared the outbreak a public health emergency of international concern on 30 January 2020, and a pandemic on 11 March 2020.³

Since the first reports in late December 2020, nearly 950 000 deaths have been attributed to COVID-19 worldwide,^{4,5} and the pandemic has become a global challenge.^{2,6} By 18 September 2020, 67 176 COVID-19 cases had been confirmed in Portugal, resulting in the deaths of 1894 persons (case fatality rate of confirmed cases 2.8%).⁷

The influence of medication use on the clinical course of COVID-19 patients admitted to hospital facilities is currently being studied as part of a multinational cohort study including several hospitals from across Europe (known as the COVID-19 Medication (COMET) study).⁸

Among possible therapies, hydroxychloroquine (HCQ), alone or in combination with other drugs, such as azithromycin (AZ) or lopinavir/ritonavir (LPV/r), was used off-label for the treatment of COVID-19, based on its immunomodulatory and antiviral properties, despite an absence of methodologically appropriate proof of its efficacy.^{6,9} Several observational studies related to COVID-19 reported an association between the use of either chloroquine or HCQ and significant cardiovascular risks, a well-known side effect of such treatments, including cardiac arrhythmias and cardiac arrest.¹⁰⁻¹² The Portuguese National Authority for Medicines and Health Products (INFARMED) issued a statement on 24 April 2020, recommending that its administration should be carried out exclusively in a hospital environment under medical supervision; equally, all plausible adverse reactions should be reported to the competent authority. On 28 May 2020, the INFARMED together with the National Health Authority (DGS) recommended discontinuing the use of HCQ in patients with COVID-19 owing to the lack of efficacy data to support its use.¹³ It has come to our attention that in some trials, including the WHO's large multinational Solidarity trial, patient enrolment into trial arms with HCQ and LPV/r has been suspended.¹⁴



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Patients and healthcare professionals were reminded all along to report any suspected side effects to their national regulatory authorities.¹³

In June 2020, the Human Medicines Committee (CHMP) of the European Medicines Agency (EMA) granted conditional marketing authorisation to remdesivir (REM) for the treatment of COVID-19 in adults and adolescents (≥ 12 years of age) with pneumonia who require supplemental oxygen. REM became therefore the first approved therapeutic option for COVID-19. Data on REM was assessed in a brief timeframe through a rolling-review procedure, an approach used by the EMA during public health emergencies to evaluate data as they became available. Based mainly on data from the NIAID-ACCT-1 study (NCT0428075), REM demonstrated superiority to placebo in shortening the time to recovery in hospitalised adults with COVID-19 and evidence of lower respiratory tract infection.¹⁵ The most common non-serious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate (GFR), increased blood creatinine levels, haemoglobin levels and lymphocyte count, respiratory failure, anaemia, fever and increased blood glucose levels.¹⁵

Considering that observational research is an essential mainstay in off-label use and post-marketing surveillance of treatments, the study reported here evaluates the suspected adverse drug reactions (ADRs—their type and incidence) associated with REM- and HCQ-based regimens in patients with COVID-19 reported to the Portuguese Pharmacovigilance System over 6 consecutive months.

METHODS

Study design and population

A prospective, observational cohort study was carried out from 16 March to 15 August 2020. Patients were assessed for eligibility based on a positive reverse transcriptase-polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 in a respiratory tract sample and treated with either REM or HCQ alone or in combination with other medications. Patients prescribed HCQ or LPV/r for labelled indications were excluded from active monitoring and therefore from the analysis reported here. The study followed the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by our Hospital Centre Ethics Committee.

Active monitoring

A chart review of patients who met the inclusion criteria was carried out to determine the occurrence of ADRs as per the active monitoring model used in our institution. A team of reviewers was created for this effect (ADRinCOV team). The ADRinCOV team checked prospectively the medical records one by one for relevance evaluation. The action triggered as a result of the occurring ADR was evaluated, namely drug discontinuation, temporary suspension or no particular action. Suspected ADRs were reported to the Portuguese Pharmacovigilance System using its online tool (Portal RAM at <https://www.infarmed.pt/web/infarmed/portalram>). The Portuguese National Pharmacovigilance System team was in charge of assessing the causality between the drug and the suspected ADR.¹⁶

Statistical analysis

Participants who fulfilled the eligibility criteria were divided into two cohorts: those prescribed HCQ regimens, and those given REM. The ADR cumulative incidence was compared between the two cohorts using the Statistical Package for Social Science

(SPSS) version 26.¹⁷ The statistical methodology of univariate and bivariate descriptive analysis was applied. Measures of central tendency, measures of dispersion and shape (quantitative variables), as well as the relative and absolute frequencies (qualitative variables) were determined. The statistical association between variables was assessed using χ^2 and Fisher's exact test, as applicable. A value of $p < 0.05$ was considered significant.

RESULTS

We conducted a chart review of the entire sample of 149 participants. Of these, 101 were on an HCQ regimen (400 mg on day 1, followed by 200 mg twice daily for 5–10 days) while the remaining 48 took REM (200 mg on day 1 followed by 100 mg once daily for 5 or 10 days). Of the 101 participants prescribed HCQ, 20 (13.4%) of them took it alone, 52 (34.9%) in combination with AZ, 22 (14.8%) with LPV/r, and seven (4.7%) with both LPV/r and AZ.

There were more male participants in both cohorts (56.4% and 68.8% in the REM and HCQ, respectively). Mean age was 65.5 ± 15.7 years and 62.0 ± 17.0 years for the HCQ and REM cohorts, respectively. In regard to smoking status, 'never smoked' was the most frequently reported status. Underlying primary diseases (asthma, cancer, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes and HIV) were present in 77.2% of patients in the HCQ cohort and 77.1% of patients in the REM cohort. Unlike in the REM cohort, the majority of patients in the HCQ cohort were overweight or obese (58.1%). When COVID-19 therapy was introduced, the average number of medications prescribed was 7.7 ± 3.2 in the HCQ cohort versus 6.7 ± 2.7 in the REM cohort, during hospital stays of 21.9 ± 13.8 days and 23.0 ± 14.1 days, respectively. Both cohorts did not differ significantly in regard to the analysed characteristics, except for medication at baseline with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB) and coexistence of chronic kidney disease. Body mass index (BMI) was at the threshold of statistically significant difference. (table 1)

A total of 102 ADRs were identified during the study period. The average time for the occurrence of an ADR was 3.9 days, with onset ranging from day 1 after starting HCQ therapy to 12 days, while this occurred between 2 and 7 days for those ADRs reported in patients taking REM. ADR incidence was significantly higher in the HCQ cohort (47.5%) than in the REM (12.5%) cohort ($p < 0.001$). This trend was also observed after stratifying data by gender, age, medication at baseline and BMI.

We found a statistically significant difference between HCQ and REM in male and female patients, in the age range between 60–79 years, the ACE inhibitor/ARB subgroup, and in the two BMI categories. Similar distributions were observed for comorbidities but, due to the reduced number of patients studied, only diabetes and hypertension could be evaluated (table 2). Nevertheless, only the latter showed a statistically significant difference ($p < 0.001$). Finally, the small number of patients precluded the comparison between groups for smoking status (table 2).

The ADR incidence across the different drug regimens is presented in table 3.

Of the 149 patients, 54 (36.2%) had one or more suspected ADRs. Hepatobiliary disorders were identified in 43 (28.9%) patients corresponding to the most common ADR, followed by gastrointestinal (18.8%), renal (6.0%) and cardiac (5.4%) disorders. Within hepatobiliary disorders, transaminase increase was present in 51.2% of patients. Except for ADRs relating to nervous system disorders, which were reported only once in the

Table 1 Characteristics of patient cohorts exposed to HCQ and REM

Characteristics	HCQ patients	REM patients	P value
	n=101	n=48	
Age, years	65.5±15.7	62.0±17.0	0.147
<40–59	35 (34.6)	16 (33.3)	0.874
60–79	42 (41.6)	25 (52.1)	0.229
≥80	24 (23.8)	7 (14.6)	0.197
Gender			
Male	57 (56.4)	33 (68.8)	0.151
Female	44 (43.6)	15 (31.2)	
Coexisting conditions			
Asthma	6 (5.9)	0	
Cancer	16 (15.8)	8 (16.7)	0.898
Chronic kidney disease	19 (18.8)	1 (2.1)	0.005
Diabetes	32 (31.7)	13 (27.1)	0.567
HIV/AIDS	6 (5.9)	1 (2.1)	0.531
Hypertension	52 (51.5)	27 (56.3)	0.586
Medication (at baseline)			
ACE inhibitor or ARB	31 (30.7)	23 (47.9)	0.040
Immunosuppressive drugs	9 (8.9)	1 (2.1)	0.227
Drugs at antiviral prescription	7.7±3.2	6.7±2.7	0.723
Drugs during hospital stay	21.9±13.8	23.0±14.1	0.602
Body mass index	n=86	n=48	
Normal/underweight	36 (41.9)	28 (58.3)	0.060
Obese/overweight	50 (58.1)	20 (41.7)	
Smoking status	n=68	n=20	
Past smoker	23 (33.8)	7 (35.0)	0.977
Smoker	6 (8.8)	2 (10.0)	
Never smoked	39 (57.4)	11 (55.0)	
Hospital stay, days	22.0±20.9	18.0±11.33	0.305

Data are shown as mean±SD or n (%).

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; HCQ, hydroxychloroquine; REM, remdesivir.

REM cohort, the ADR incidence was greater in the HCQ group, which included QT interval prolongation in six patients and atrial fibrillation in two patients. The HCQ+LPV/r subgroup reported the higher number of hepatobiliary (86.4%) and renal (27.3%) disorders.

ADRs were categorised according to the action carried out: 'severe' if drug discontinuation occurred; 'moderate' if there was a temporary suspension; and 'mild' if no particular action was performed. Drug discontinuation was observed in 21 patients (three REM, 18 HCQ), temporary suspension of therapy in 10 (two REM, eight HCQ) and no particular action was taken in 23 patients (one REM, 22 HCQ). Drug discontinuation was observed in 21 (38.9%) patients, temporary suspension of therapy in 10 (18.5%) and no particular action was taken in 23 (42.6%) patients. Causality was assessed in 81 ADRs, revealing that none was certain or definitive, yet all were considered possible. The unlabelled adverse drug events occurred in the HCQ+AZ (n=1) and HCQ+LPV/r (n=7) subgroups.

DISCUSSION

Studies reporting drug safety monitoring in patients with COVID-19 are scarce.^{10–17} As far as we know, this is the first population-based study conducted to evaluate the safety of REM and HCQ in COVID-19 patients in real-world clinical practice, providing information for patients, physicians and drug safety regulators. Here we investigated the ADR incidence in patients treated with either HCQ or REM, alone or combined with other

Table 2 Incidence of ADRs in patients exposed to HCQ and REM

Characteristics	HCQ patients	REM patients	P value
	n=101 (%)	n=48 (%)	
Total	48 (47.5)	6 (12.5)	<0001
Age, years			
<40–59	16/35 (45.7)	4/16 (25.0)	0.160
60–79	20/42 (47.6)	2/25 (8.0)	<0001
≥80	12/24 (50.0)	0/7 (0.0)	0.017
Gender			
Male	28/57 (49.1)	5/33 (15.2)	0.001
Female	20/44 (45.4)	1/15 (6.7)	0.006
Coexisting conditions			
Asthma	2/6 (33.3)	0/0 (0.0)	
Cancer	6/16 (37.5)	0/8 (0.0)	
Chronic kidney disease	9/19 (47.4)	1/1 (100)	
Diabetes	12/32 (37.5)	2/13 (15.4)	0.146
HIV/AIDS	2/6 (33.3)	1/1 (100)	
Hypertension	27/52 (51.9)	3/27 (11.1)	<0001
Medication (at baseline)			
ACE inhibitor or ARB	18/31 (58.1)	3/23 (13.0)	<0001
Immunosuppressive drugs	5/9 (55.6)	0/1 (0.0)	
Body mass index	n=86	n=48	
Normal/underweight	15/36 (41.7)	2/28 (7.1)	0.001
Obese/overweight	30/50 (60.0)	4/20 (20.0)	0.002
Smoking status	n=68	n=20	
Past smoker	12/23 (52.2)	2/7 (28.6)	
Smoker	2/6 (33.3)	0/2 (0.0)	
Never smoked	21/39 (53.8)	1/11 (9.1)	

ACE, angiotensin-converting enzyme; ADRs, adverse drug reactions; ARB, angiotensin-receptor blocker; HCQ, hydroxychloroquine; REM, remdesivir.

medications. Over the study period, the number of HCQ-treated patients was greater than REM-treated patients, given REM only became available for prescription outside clinical trials from June 2020.

Obesity, a known risk factor for respiratory infection, is increasingly being recognised as a predisposing factor in the COVID-19 pandemic.^{18–21} Previous studies that set out to evaluate risk factors in viral pandemics have shown that obesity, particularly severe obesity (BMI >40 kg/m²), is associated with increased risk of hospitalisation, critical care admission and fatalities, and that obese individuals have a greater than sixfold increase in odds of hospitalisation compared with adults of normal weight.^{18–21} Unlike in the REM cohort, the majority of patients in the HCQ cohort were overweight or obese, and had a higher frequency of ADRs (58.1% vs 41.7%). As far as we are aware, no association has been formally established between obesity as a risk factor for ADRs in patients with COVID-19 and treatment with either HCQ or REM.^{18–21} Given that HCQ is no longer recommended for the treatment of COVID-19, we trust that the increasing pool of data collected for REM will allow us to better establish the safety of this drug in patients with obesity.

Both cohorts did not differ significantly in regard to the analysed characteristics, except for medication at baseline with an ACE inhibitor or an ARB and coexistence of chronic kidney disease. There was only one patient with concomitant chronic kidney disease in the REM group. This can be explained by the fact that the pharmacokinetics of REM have not been evaluated in patients with renal impairment. In fact, REM is contraindicated in patients with an estimated GFR <30 mL/min.²²

Table 3 ADR incidence by drug regimen

	All regimens n=149	HCQ n=20	HCQ+AZ n=52	HCQ+LPV/r n=22	HCQ+AZ+LPV/r n=7	HCQ regimens n=101	REM n=48
Hepatobiliary disorders	43 (28.9%)	2 (10.0%)	11 (21.2%)	19 (86.4%)	7 (100%)	39 (38.6%)	4 (8.3%)
↑ Transaminases	22	2	2	12	3	19	3
↑ Bilirubin	5	0	0	3	1	4	1
↑ GGT	5	0	1	3	1	5	0
Liver cholestasis	6	0	4	1	1	6	0
Hepatotoxicity	5	0	4	0	1	5	0
Other							
GI disorders	28 (18.8%)	4 (20.0%)	6 (11.5%)	12 (54.5%)	6 (85.7%)	28 (27.7%)	0
Diarrhoea	16	1	1	9	5	16	0
Nausea	6	2	2	1	1	6	0
Vomiting	3	1	1	1	0	3	0
Other GI disorders	3	0	2	1	0	3	0
Acute renal failure	9 (6.0%)	0	2 (3.8%)	6 (27.3%)	0	8 (7.9%)	1 (2.1%)
Cardiac disorders	8 (5.4%)	2 (10.0%)	4 (7.7%)	0	2 (28.6%)	8 (7.9%)	0
↑ QT interval	6	2	3	0	1	6	0
AF	2	0	1	0	1	2	0
Blood and lymphatic system	2 (1.3%)	0	0	2 (9.1%)	0	2 (2.0%)	0
Thrombocytopenia	1	0	0	1	0	1	0
Lymphopenia	1	0	0	1	0	1	0
Skin and subcutaneous	3 (2.0%)	2 (10.0%)	1 (1.9%)	0	0	3 (3.0%)	0
Ocular	2 (1.3%)	0	1 (1.9%)	1 (4.5%)	0	2 (2.0%)	0
Nervous system	1 (0.7%)	0	0	0	0	0	1 (2.1%)
Other	6 (4.0%)	0	1 (1.9%)	4 (18.2%)	0	5 (5.0%)	1 (2.1%)

ADR, adverse drug reaction; AF, Atrial fibrillation; AZ, azithromycin; GGT, gamma-glutamyl transferase; GI, gastrointestinal; HCQ, hydroxychloroquine; LPV/r, lopinavir/ritonavir; REM, remdesivir.

The average time for the occurrence of an ADR was 3.9 days. We verified that the onset of ADRs in the HCQ group was similar to that reported in the literature.^{17,23} Regarding REM, the time elapsing since it was first administered until the ADR was clinically noticeable ranged from 2–7 days. We were unable to corroborate this finding due to the lack of data reported in the literature.

The incidence of ADR in patients taking HCQ regimens (alone or in combination) mainly manifested as hepatobiliary and gastrointestinal disorders, as found by others.^{17,23} As similarly reported by another research group, we also found QT interval prolongation in six patients and atrial fibrillation in two patients, further contributing to support the well-described cardiotoxicity related to HCQ regimens.⁶ Despite toxicity to the eye being generally related to HCQ long-term use,^{17,23} ocular disorders were reported for two patients even though, in this study, treatment duration was on average <10 days. However, contrary to what happens with long-term use of this medication, systematic screening of ophthalmic changes caused by HCQ has not been performed in our case.²⁴ Finally, it is important to mention that the LPV/r subgroup seems to be associated with an increased likelihood of adverse drug events.^{17,25}

We found a lower incidence of ADRs for REM (14.6% vs 23%) compared with other authors²²; however, this may be explained by the small sample size in our study owing to REM being available for labelled prescription towards the end of the study period. Other factors that might have contributed to explain this lower incidence relate to the study design (eg, how study stratification was carried out) or the stricter prescribing criteria established for this medication. As mostly seen in other studies,^{15,22} liver disorders and acute renal failure were likewise reported in our research. Surprisingly, we also found ADRs related to the central

nervous system (convulsion in one patient) and a case of seroma, none of which had been previously described as potential ADRs of REM.^{15,26} The ongoing collection of safety data from patients enrolled in the study (the total number of which was 255 at the time of submission of the present report) will allow us to better evaluate the safety profile of REM in patients with COVID-19 and whether there are populations particularly at risk of ADRs linked to this new treatment.

The incidence of ADRs was significantly higher in the HCQ cohort when compared with the REM cohort. These results are not to be compared with other studies since none of the drug regimens reported here was used throughout the study period of 6 months (HCQ was prescribed between 3 March 2020 and 13 June 2020, coinciding with the recommendation against its use in this indication, while REM was prescribed from 20 June 2020, after it was first granted authorisation for use in this indication). In this study, all ADRs were described as ‘possible’, which is in line with results reported in other studies.¹⁷ Once adverse reactions are rarely drug-specific, the most frequent categories in the literature are ‘possible’ and ‘probable’. Diagnostic tests are usually absent, and a (re)challenge is rarely ethically justified.¹⁶

Our study contributes to the body of evidence that monitoring ADRs is important for COVID-19 patients. First, the active monitoring model implemented by the Centro Hospitalar de Lisboa Ocidental has proved effective in quantifying the incidence of ADRs. Second, the study approach focused not only on the off-label prescription used at the beginning of the pandemic but also on the single authorised drug for COVID-19 thus far. Third, we found that in 38.9% of patients (21 patients in total, 18 on HCQ and three on REM), the clinical significance of the reported ADRs was sufficient to result in definitive discontinuation of the patients’ medication regimens.

Noteworthy is the identification of eight unlabelled ADRs (gastric stasis in two patients, one treated with HCQ+AZ and the other with HCQ+LPV/r, and acute renal failure in six patients treated with HCQ+LPV/r), since one of the principal foundations of pharmacovigilance is the detection of unknown and unexpected adverse reactions.

Our study has some potential limitations. We studied a relatively small number of patients, some of whom were discharged before completing their HCQ course. Since ADR monitoring was conducted exclusively during the hospital stay, it is possible that ADRs went under-reported. Besides, no follow-up of reported ADRs was carried out.

CONCLUSIONS

The preliminary results reported here show that establishing pharmacovigilance networks, particularly for new drugs prescribed to patients who are often comorbid, as is the case for REM in COVID-19 patients, is essential to assure safe medical care in the real world. The safety data provided for REM contributes to strengthening the body of evidence to support its safe use in COVID-19 patients. Although the data presented here point towards a safer and more manageable safety profile of REM, only the ongoing systematic collection of data from all patients meeting the inclusion criteria will allow its safety in real-world practice to be determined. Information on whether the implementation of active surveillance methods has a measurable impact on clinical outcomes and on how ADRs evolve during the patient's clinical course has not yet been determined for therapeutic regimens, old and new, used in this context, and should therefore be encouraged.

What this paper adds

What is already known on this subject?

- Safety concerns have been raised linked to COVID-19 therapies since the beginning of the pandemic, which led to changes in the therapeutic approach of patients over time. Real-world data are critical to establish the drug safety profile.
- Active monitoring has the power to identify adverse drug reactions (ADRs) far superior to spontaneous reporting and, along with active pharmacovigilance, it becomes essential when considering off-label use, recently approved drugs or new therapeutic indications, given the possible limited evidence.

What this study adds

- Our objective was to evaluate ADRs related to remdesivir- or hydroxychloroquine-based regimens in COVID-19 patients in a Portuguese hospital centre.
- The study methodology used, based on an active monitoring model, focused not only on the off-label prescription used at the beginning of the pandemic, but also on the single authorised drug for COVID-19, allowing us to quantify the incidence of ADRs.

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