



## Serious adverse drug reactions with hydroxychloroquine: a pharmacovigilance study in Vigibase®

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Hydroxychloroquine is a chloroquine derivative, widely used in rheumatoid arthritis or lupus [1]. Following pilot observational studies, it has been recently proposed (alone or with azithromycin) in COVID-19 patients despite lack of clinical evidence [2, 3]. Using an old drug in a new disease means evaluation of benefits but also risks. Although several adverse drug reactions (ADRs) were described with hydroxychloroquine, there are no general data about their relative frequency and occurrence. Recent development of large databases in pharmacovigilance offers new opportunities to investigate the safety profile of such candidate drugs [4]. It was the aim of this study to investigate the safety profile of hydroxychloroquine (alone or with azithromycin).

The study was performed in Vigibase®, the WHO pharmacovigilance database, which registers all Individual Case Safety Reports (ICSRs) from more than 130 countries [5]. We extracted all ICSR registered as “serious” and “suspected/interacting” between 1 January 2010 and 31 December 2019 and including men or women aged  $\geq 18$  years. ICSR in patients with age and sex unknown or registered as malformations, medication errors, or treatment failure were excluded. We describe the main characteristics of patients (age, sex) and kind of ADRs (classified according to Standardized MedDRA Queries (SMQs), classification). A special attention was given to lethal ICSR and those with hydroxychloroquine + azithromycin (H+A) [2].

There were 5219 ICSR in Vigibase®, 82.1% in women, mean age  $54.3 \pm 15.4$  [18–95], 25.6% between 18 and 64 years, 46.5% between 45 and 64 years, 19.2% between 65

and 74 years, and 8.7%  $\geq 75$  years. Hydroxychloroquine indication was known in around 80% ICSR: 37% in rheumatology, 21% in dermatology. The 3 main SMQs were hypersensitivity/allergic reactions, arthralgia and gastrointestinal ADRs. Retinal toxicity was found in 6.7% of ICSR, cardiac arrhythmias (including 1.6% torsades de pointes/QT prolongation) in 5.0%, cardiomyopathy in 3.3% (Table 1). Deaths were reported in 221 patients (4.2%), mainly women (76.0%), 43.0% between 45 and 64 years. The first origin was cardiac disorders ( $n = 79$ ). We found 65 poisonings, and 62 psychiatric and 54 respiratory disorders. Only 9 reports involved H+A with 2 anaphylactic reactions without any death.

The present was performed to precise “serious” ADRs with hydroxychloroquine. It is the first study investigating these data in a worldwide perspective. The main ADRs were hypersensitivity and allergic reactions, arthralgia, and skin disorders. We also found the well-known ocular toxicity of hydroxychloroquine after long-term use. Too few ADRs were reported with H+A to allow any definite conclusion.

The most interesting results are the relative high percentage of cardiac ADRs (cardiomyopathy + arrhythmias = 8.3% of total ICSR) showing that hydroxychloroquine, first, possesses a direct myocardial toxicity and, second, can disturb cardiac rhythm. The fact that reported deaths were more than one out of three times from cardiac origin is in agreement with this conclusion. The narrow therapeutic range of hydroxychloroquine [1] also explains the relative high percentage of poisoning. The present results also show that the cardiac signal (QT prolongation, arrhythmias...) found with hydroxychloroquine in COVID-19 patients [5, 6] was already present in patients with rheumatoid arthritis or lupus.

Another interesting result is the psychiatric ICSR: 1.7% depression, 1.7% suicide, 1.3% psychosis. This could be another pharmacovigilance signal as recently suggested by the Spanish and French drug agencies [7].

Although suffering from the mandatory biases of such studies (underreporting, lack of systematic information on doses and duration exposure in Vigibase®, denominator

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**Table 1** “Serious” Individual Case Safety Reports (ICSRs) registered in Vigibase® between 1 January 2010 and 31 December 2019 according to Standardised MedDRA Queries (SMQs) classification

Number of “serious” ICSRs, SMQ (narrow) > 1%	5219	100.0%
Hypersensitivity	1229	23.5%
Arthralgia	882	16.9%
Gastrointestinal (nausea, vomiting, diarrhea, constipation)	727	13.9%
Haemodynamic_oedema, effusions, fluid overload	517	9.9%
Retinal	348	6.7%
Cytopenia	328	6.3%
Non_infectious_diarrhea	253	4.8%
Haemorrhage	216	4.1%
Angioedema	215	4.1%
Infective_pneumonia	209	4.0%
Shock	194	3.7%
Cardiac_arrhythmias	180	3.4%
Cardiomyopathy	172	3.3%
Embolic_thrombotic_event	158	3.0%
Cardiac_failure	143	2.7%
Interstitial_lung	132	2.5%
Arterial_hypertension	129	2.5%
Agranulocytosis	118	2.3%
Hearing	116	2.2%
Gastrointestinal_perforation	112	2.1%
Acute_renal_failure	102	2.0%
Depression	90	1.7%
Suicide	89	1.7%
Torsades de pointes/QT prolongation	86	1.6%
Rhabdomyolysis	71	1.4%
Psychosis	66	1.3%
Respiratory_failure	65	1.2%
Acute_central_respiratory_depression	55	1.1%

unknown, use of hydroxychloroquine in rheumatic or autoimmune disorders and not COVID-19), the results have several important strengths: data in the context of real world not studied in clinical trials, study performed in the world’s largest pharmacovigilance database from around 130 countries allowing generalization of results.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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