COMMENTARY ARTICLE

Clinical Pharmacists role in the therapeutic management of COVID-19 patients in Morocco

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Abstract

In Morocco, the first case of a respiratory illness due to a new form of coronavirus, the SARS-CoV-2, was registered on the evening of March 1st according to the Ministry of Health.
As the pandemic threatened to develop, the Technical and Scientific Committee of the Ministry of Health decided to prescribe a combination of chloroquine/ hydroxychloroquine with azithromycin for all symptomatic patients confirmed COVID-19 in spite of the fact that the combination has not been approved for COVID-19 indication.
This off-label use exposes to an iatrogenic risk. The aim of this paper is to establish an integrated strategy for pharmaceutical care services which a focus on COVID-19 hospitalized patients (excluding patients in intensive care units) and Clinical Pharmacists, in order to improve COVID-19 patients' outcome, reduce mortality and drug-related iatrogenia and facilitate pandemic control.
Clinical Pharmacists have played an important role in optimizing the management of COVID-19 patients within the hospital structure from the admission to the discharge of patients. Clinical Pharmacists participate in the therapeutic decision, manage drug Interactions and adjust therapy for special risk population and patients with combined underlying diseases. They also monitor and evaluate medication safety (Medication errors, drug interactions and adverse drug reactions). They have developed practical help sheets that constitute a reliable, and "easy to search" database.
During this crisis, Clinical Pharmacists have not only developed protocols and practical sheets but they have also been the guarantors of the rational use of drugs, providing medical advice to frontline medical staff, especially regarding off label drugs.

Keywords: Clinical Pharmacist; Hydroxychloroquine; Azithromycin; COVID-19; Iatrogenia; Drug interactions.

1. Introduction:

In December 2019, a respiratory illness due to a new form of coronavirus, the SARS-CoV-2, was first identified in China [1]. In Morocco, the first case was registered on the evening of March 1st according to the Ministry of Health [2]. The respiratory illness due to SARS-CoV-2, named COVID-19, has now developed into a worldwide pandemic and poses a major challenge to global public health systems [3].
For confirmed COVID-19 cases, reported illnesses have ranged from people with little to no symptoms to people being severely ill and dying. On admission to hospital, symptoms may include: Fever (over 80% of the patients), Cough (over 80%), Shortness of breath (31%), Muscle ache (11%)[4]. There is a higher risk of mortality for elderly patients and for patients who suffer from comorbidities such as hypertension or diabetes[5]. The SARS-CoV-2 has an incubation period of 2 to 14 days before the outbreak of these symptoms [6].
Currently, there is no specific medicine or vaccine for COVID-19 fully tested for safety and efficiency[7].A number of drugs approved for other indications and available in the Moroccan market are of great interest for the COVID-19 treatment. However, data

supporting the use of these agents is often limited to in vitro studies, animal models, or case series[8].

If these agents are used, this off-label use exposes to an iatrogenic risk. Therefore, Clinical Pharmacists play an essential and unique role within the healthcare team in optimizing patient care during this COVID-19 pandemic.

In Morocco, the implementation of Clinical Pharmacy at the Ibn Sina University Hospital Center (CHU) of Rabat began in September 2017 with the full-time appointment of a Clinical Pharmacist in a different department. Clinical Pharmacist interventions have demonstrated a positive clinical impact regarding prescriptions review, optimization of drugs administration and guidelines development [9-12].

The aim of this paper is to establish an integrated strategy for pharmaceutical care services which a focus on COVID-19 hospitalized patients (excluding patients in intensive care units) and Clinical Pharmacists, in order to improve COVID-19 patients' outcome, reduce mortality and drug-related iatrogenia and facilitate pandemic control.

1.1 Current context of scientific data for chloroquine/hydroxychloroquine and azithromycinActivity and mechanisms of action:

While no agents are currently Food and Drug Administration (FDA) approved for the COVID-19 treatment, a number of drugs approved for other indications are being studied in several hundred clinical trials worldwide[13].

Based on their experimental properties, chloroquine (CQ) and especially its analog hydroxychloroquine (HCQ) in addition to azithromycin (AZT) have been suggested and tested by several groups of researchers for their potential against novel coronavirus.

Hydroxychloroquine and chloroquine are oral prescription drugs that have been used for the treatment of malaria and certain inflammatory conditions. Both drugs have in-vitro activity against SARS-CoV-2, and other coronaviruses, with hydroxychloroquine having relatively higher potency against SARS-CoV-2 [13].

Little is currently known about the mechanisms of action of CQ/ HCQ in the treatment of SARS-CoV-2 infection. Wang and colleagues found that CQ blocked infection at both entry and post-entry steps. They suggest that the drugs block endocytotic vesicle maturation at intermediate stages and probably stall the virus transport from EEs to LELs, a crucial step for the release of viral genome [14].Another studies revealed that it works by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV [13]. Another therapeutic drug is the Azithromycin, which is an antibiotics widely used to treat respiratory infections. This drug was shown to have therapeutic effects against COVID-19. In a Mexican study, the researchers were able to prove that azithromycin acted as an acidotropic lipophilic weak base which modulate the pH of endosomes and trans-Golgi network. This further led to in vitro effects on intracellular organelles similar to the one conferred by hydroxychloroquine [15].

The clinical efficiency of the combination of HCQ/CQ and AZT against COVID-19 has become a very controversial issue in the medical community. Translation from laboratory to clinic should be based on detailed analysis of results from randomized controlled studies to understand the real effectiveness

[16].Indeed, recent clinical studies addressing the efficiency of HCQ and azithromycin were conducted in COVID-19 patients leading to contradictory results.

Additionally, a recent meta-analysis reported the effect of HCQ on viral clearance and mortality outcome, compared to the placebo. In this Study, no benefit of HCQ in the treatment of COVID-19 was found and there was a two-fold increase in deaths compared to the control arm. A purported benefit of HCQ/HQ in early or mild COVID-19 was observed in studies by Chen et al.[17] and Gautret et al.[18] and was included in the result of this meta-analysis[19]. Except for one elderly patient who arrived with an advanced form, clinical improvements were observed in all cases in an uncontrolled, non-comparative, observational study in a cohort of 80 relatively mildly infected patients treated with a combination of HQ and AZT [13]. HCQ may therefore have some benefits in early and mild COVID-19 but possibly be harmful in moderate to severe COVID-19[19].

Further research using large cohort of samples with randomized controlled clinical trials are urgently required for each drug alone and in-combination in order to find a concrete solution against COVID-19 infection.

1.2 Risks:

When therapeutic agents such as hydroxychloroquine and azithromycin are being considered, we must also focuses on the potential harms[20].HCQ/CQ and AZT have each been independently shown to increase the risk for QT interval prolongation, drug-induced torsade de pointes (TdP), and sudden cardiac death (SCD) [21]

Emerging studies from France and USA have increasingly cautioned for QTc prolongation with both HCQ and HCQ plus AZT. While Bessiere et al. [22]reported a prolonged QTc in 93% of the patients receiving either HCQ or HCQ plus AZT; Mercuro et al.[23] reported QTc prolongation in 20% of patients treated with HCQ alone or HCQ plus AZT.While no benefit on viral clearance demonstrated by HCQ compared to the control in patients with COVID-19, these findings underscores the toxicity of this drugs combination and warrants its use with an extreme caution.[19]

CQ and HCQ are extremely well-known drugs which have already been prescribed to billions of people [24]. However, a failure to consider harms in research could be detrimental to the patient. A drug may be relatively safe for one medical condition but unsafe for another and as such, must be carefully examined [20].

1.3 Moroccan recommendations:

Nevertheless, based on these limited observational and anecdotal evidence, several guidelines across the world allowed both these drugs in the treatment of COVID-19 [19]

In Morocco, the Technical and Scientific Committee of the Ministry of Health decided to prescribe chloroquine/ hydroxychloroquine in combination with azithromycin for all symptomatic patients confirmed COVID-19 as of 23rd March, 2020 [13].

Another ministerial circular extend the use of this combination to patients highly suspected of COVID-19 disease while waiting for the test result.

The dosing regimen in both circulars was as follow [25]:

CQ 500mgx2 per day or HCQ 200mg x3 per day for 10 days with Azithromycin 500mg first day and 250mg from day 2 to day 7.

Moroccan Government has maintained its recommendations about the use of CQ/ HCQ in combination with AZT despite the last

article in the lancet[26] suggesting an excess mortality linked to these drugs, especially in severe forms of the disease.

2. The role of the clinical pharmacist in managing the crises

2.1 Development of prescription aid and monitoring tools:

In view of the context, the Clinical Pharmacy team has developed practical prescription help sheets that summarize essential points to be known before admitting a patient in the COVID-19 therapeutic protocol.

These sheets are intended for internal physicians and residents embedded in COVID-19 hospital care units and include:

1. Two practical sheets dedicated to the two molecules of the therapeutic protocol HCQ / CQ and AZT:
   - Action mechanism of QC / HCQ and AZT assumed in SARS-COV2;
   - Dosage recommended by the Ministry of Health in the care of the COVID-19 patients;
   - Terms of administration in normal situations and in the event of swallowing disorders;
   - Main pharmacokinetic characteristics of these molecules (bioavailability,C_{MAX},$T_{1/2}$,…);
   - Mechanism and management of cardiac risk: lengthening of the QT space and risk of torsade de pointes, methods of ECG monitoring and monitoring of serum potassium
   - Management of other undesirable effects (digestive, haematological ...);
   - Absolute and relative contraindications ;
   - Potential drug interactions.
2. A practical sheet on drugs that prolong QT and induce TdP:

Drugs proposed in the management of patients infected with covid-19 are associated with a risk of prolongation of the QT interval. This risk is increased in the presence of certain factors, in particular during drug interactions[27] . Clinical Pharmacists have developed a practical sheet, which constitutes a decision tool in the event of the prescription of other molecules in order to minimize the risk of prolongation of the QT interval.

This fact sheet summarizes the factors that increase the risk of QT/TdP. It classifies the drugs marketed in Morocco in three categories according to credibleMeds:

- Categorie 1 : Known Risk of TdP - These drugs prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended: in case of need of association with the CQ/HCQ and AZT, practitioners should evaluate the benefit / risk.
- Categorie 2: Possible Risk of TdP - These drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended. Also, practitioners should evaluate the benefit / risk in such a situation.
- Categorie 3: Conditional Risk of TdP - These drugs are associated with TdP BUT only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) or by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP): In that case, physician are required to contact Clinical Pharmacists in order to identify the cause of the drug interaction,

check the prescribed dosage taking into account the pathophysiological condition of the patients or correct the hydro-electrolytic disorders. A decision is then made upon evaluation of the benefit/risk.

3. Practical sheet on antiemetic drug: Nausea and vomiting are among the clinical symptoms [28] of the COVID-19 infection and may also be part of the treatment's side effects [29]. Most antiemetics to be prescribed carry a risk of prolongation of the QT interval [30].Clinical Pharmacists have established a practice sheet on antiemetics that can be associated with the COVID-19 protocol without risk of QT/ TdP. This profile focuses on lifestyle and dietary rules.
4. Patients under COVID-19 treatment monitoring sheet: the objective is to help Clinical Pharmacists monitor patients under COVID-19 therapeutic protocol and easily identify the occurrence of adverse effects. The monitoring sheet includes:
    - Patient's comorbidities;
    - Concurrent drugs involving the prolongation of the QT space;
    - ECG monitoring: QTc prior to treatment initiation;
    - Tisdale score to evaluate the risk of rythm disorder and determine monitoring frequency[31];
    - Biological check-up to monitor potential hydro-electrolytic or haematological disorders as well as the patient's renal and hepatic function. ECG monitoring at H4, J2, J9 and whenever deemed necessary depending on the patient's condition.

2.2 Clinical Pharmacists Interventions on the healthcare team

Clinical Pharmacists are an essential link within the special COVID care unit[8] :

Upon patients' admission: they check medical history in order to know the patient's profile, chronic treatments, list of comorbidities and possibly those involving the prolongation of the QT interval. Clinical Pharmacists also check out all biological parameters (renal and hepatic function, blood counts). During the daily staff meeting, the healthcare personnel discuss treatment strategies, medical care of all hospitalized patients, confirmed or suspected of being infected with SARS-COV2. As medication expert, Clinical Pharmacists give their advice on the inclusion or non-inclusion of patients in the therapeutic protocol, taking into account contraindications and medical interactions (eg. patient with a liver failure, patient under amiodarone for a rhythm disorder). During hospitalization: Clinical Pharmacists monitor all patients' biological and clinical parameters taking into account COVID-19 combined underlying diseases and high-risk patients (elderly, HTA, IRT, IH, immunosuppressed individuals). Clinical Pharmacists make sure that patients have completed their medical treatment and ECG upon leaving the hospital.

2.3 Prescription analysis and pharmaceutical interventions

The analysis takes place on a daily basis and is carried out by Clinical Pharmacists. That analysis includes the complete checking of the following parameters: doses of HCQ/AZT and other associated medication, contraindications related to the patients' risks, interactions between essential drugs, COVID-19 protocol, high risk medication test –especially those

involving the prolongation of the QT space for patients under HCQ/AZT. The analysis is carried out taking into account all biological results (hypokaliemia, increased transaminases levels, renal and hepatic disorders…) as well as clinical indicators (INR, blood glucose level, blood pressure).

Clinical Pharmacists conduct various pharmaceutical interventions following a thorough prescription analysis. Most interventions are related to; drug intake, self-medication warning, interruption of chronic disease treatment, proposition of interruption of unjustified medical treatment, dosing adjustment, reminder on rhythm monitoring and ECG.

2.4 Monitoring and evaluation of medication safety (Medication errors, drug interactions and adverse drug reactions)

Once COVID-19 treatment is started, Clinical Pharmacists begin monitoring all patients using the treatment-monitoring sheet, which is filled out on a daily basis.

Based on the parameters noted on the treatment monitoring sheet and their progress, Clinical Pharmacists quickly detect all the side effects that may appear after the administration of HCQ / AZT (eg: prolongation of the QT interval, hypokalaemia, impaired renal and/or hepatic function. Based on this data, Clinical Pharmacists offer the healthcare team a course of action.Furthermore, the clinical pharmacists reports undesirable side effects on a special COVID-19 Declaration Sheet from the Poison Control and Pharmacovigilance Centre of Morocco .That sheet is emailed during the day to the Pharmacovigilance Center.

2.5 Distribution and delivery

Clinical Pharmacists also act as a link between healthcare units and the Central Hospital Pharmacy and participate in receiving, preparing, and delivering drugs to patients. Clinical Pharmacists report to the Central Hospital Pharmacy all problems related to drugs and medical devices.

3. Discussion:

Off-label drug use without evidence of efficiency and safety based on clinical trials, may increase the incidence of adverse side effects and expose patients to increased risks of drug iatrogenia [32]. In this situation and if these drugs are used, it is the Clinical Pharmacists' role to provide accurate data to the physicians about safe drug delivery, carry out strict monitoring of adverse side effects, assess and analyze the causal relationship of adverse drug reactions [8].

Practical sheets developed by the Clinical Pharmacists team aim to minimize the iatrogenic risk linked to an off-label use. Adapted to specific hospital practices, practical sheets constitute a reliable, and "easy to search" database.

The Clinical Pharmacy team plays an important role in optimizing the management of COVID-19 patients within the hospital structure from the admission to the discharge of patients. Clinical Pharmacists participate in the therapeutic decision, manage drug Interactions and adjust therapy for special risk population and patients with combined underlying diseases. They also monitors the occurrence of undesirable side effects.

In the literature, few pharmaceutical teams have shared their experience in the management of COVID-19. Zaiwei Song et al. [3] , reported the same pharmaceutical

activities, but did not mention any practical prescribing aid or daily monitoring sheet. Pharmacists from this same team participated in two other activities; on the one hand, they provide monitoring and management of convalescent plasma therapy, but this therapy is not included in the national plan for the management of the Moroccan COVID-19. On the other hand, they provide scientific information about vaccine development, however no clinical trial was set up during the period of the crisis in our hospital.

Finally, Clinical Pharmacists also play a role in optimizing the drug distribution and delivery highlighting the need to continuously monitor drug availability and approaches to obtaining medication[8]. This is a crucial element given that drug shortages may lead to the prescription of suboptimal therapy and provoke patient harm [33] .

4. Conclusion:

During this crisis, all health professionals were bound to develop innovative and adaptive methods. Pharmaceutical care is an essential activity to optimize patient's healthcare. Clinical Pharmacists have not only developed protocols and practical sheets but they have also been the guarantors of the rational use of drugs, providing medical advice to frontline medical staff, especially regarding off label drugs.

References:

1. Li, H., et al., *Fighting against COVID-19: Innovative strategies for clinical pharmacists.* Res Social Adm Pharm, 2020.
2. *Minstère de la santé marocain :Le Maroc annonce l'enregistrement du premier cas du nouveau Coronavirus 2020* https://www.sante.gov.ma/Pages/communiqués.aspx?communiqueID=355 .*Accessed date 15 May 2020*.
3. Song, Z., et al., *Hospital pharmacists' pharmaceutical care for hospitalized patients with COVID-19: Recommendations and guidance from clinical experience.* Res Social Adm Pharm, 2020.
4. Chen, N., et al., *Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study*. Lancet (London, England), 2020. **395**(10223): p. 507-513.
5. Fang, L., G. Karakiulakis, and M. Roth, *Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?* The Lancet. Respiratory medicine, 2020. **8**(4): p. e21-e21.
6. Lauer, S.A., et al., *The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application.* Ann Intern Med, 2020. **172**(9): p. 577-582.
7. I.P.F, *FIP HEALTH ADVISORY COVID-19: GUIDELINES FOR PHARMACISTS AND THE PHARMACY WORKFORCE*, I.P. FEDERATION, Editor. UPDATED 26 MARCH 2020. p. 30.
8. JACCP, *Roles of the clinical pharmacist during the COVID-19 pandemic.* journal of american college of clinical pharmacy, 22 March 2020: p. 3.
9. Mrani Alaoui, A., et al., *Interventions pharmaceutiques dans un service d'urgences médicales : résultats de l'expérience d'un pays du Maghreb.* Le Pharmacien Hospitalier et Clinicien, 2020.
10. Fatima-Zahra, B., et al., *Administration et préparation des antibiotiques injectables: Analyse des pratiques en réanimation chirurgicale.* Le Pharmacien Hospitalier et Clinicien, 2020.
11. Moukafih, B., et al., *Impact of clinical pharmacy services in a hematology/oncology ward in Morocco.* Journal of Oncology Pharmacy Practice, 2020: p. 1078155220919169.
12. El Marnissi, S., et al., *Analyse du risque infectieux autour du patient dans l'unité d'hémodialyse de l'hôpital Ibn Sina de Rabat par application de la méthode d'analyse des modes de défaillance, de leurs effets et de leur criticité.* Néphrologie & Thérapeutique, 2020. **16**(2): p. 105-117.
13. Saqrane, S. and M.A. El Mhammedi, *Review on the global epidemiological situation and the efficacy of chloroquine and hydroxychloroquine for the treatment of COVID-19.* New

microbes and new infections, 2020. **35**: p. 100680-100680.
14. Quiros Roldan, E., et al., *The possible mechanisms of action of 4-aminoquinolines (chloroquine/hydroxychloroquine) against Sars-Cov-2 infection (COVID-19): A role for iron homeostasis?* Pharmacological research, 2020. **158**: p. 104904-104904.
15. Choudhary, R. and A.K. Sharma, *Potential use of hydroxychloroquine, ivermectin and azithromycin drugs in fighting COVID-19: trends, scope and relevance.* New Microbes and New Infections, 2020. **35**: p. 100684.
16. Quiros Roldan, E., et al., *The possible mechanisms of action of 4-aminoquinolines (chloroquine/hydroxychloroquine) against Sars-Cov-2 infection (COVID-19): A role for iron homeostasis?* Pharmacol Res, 2020. **158**: p. 104904.
17. Chen, Z., et al., *Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial.* medRxiv, 2020: p. 2020.03.22.20040758.
18. Taccone, F.S., J. Gorham, and J.-L. Vincent, *Hydroxychloroquine in the management of critically ill patients with COVID-19: the need for an evidence base.* The Lancet Respiratory Medicine.
19. Singh, A.K., et al., *"Hydroxychloroquine in patients with COVID-19: A Systematic Review and meta-analysis."*. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2020. **14**(4): p. 589-596.
20. Alexander, P.E., et al., *COVID-19 coronavirus research has overall low methodological quality thus far: case in point for chloroquine/hydroxychloroquine.* J Clin Epidemiol, 2020.
21. Chorin, E., et al., *QT Interval Prolongation and Torsade De Pointes in Patients with COVID-19 treated with Hydroxychloroquine/Azithromycin.* Heart Rhythm, 2020.
22. Bessière, F., et al., *Assessment of QT Intervals in a Case Series of Patients With Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With Azithromycin in an Intensive Care Unit.* JAMA cardiology, 2020: p. e201787.
23. Mercuro, N.J., et al., *Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19).* JAMA Cardiol, 2020.
24. Gautret, P., et al., *Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study.* Travel Med Infect Dis, 2020. **34**: p. 101663.
25. *Ministère de la santé Marocain: circulaire N°22 prescription de la chloroquine et dispensation de la CHLOROQUINE et de l'HYDOXYCHLOROQUINE au niveau des établissements de soins* 23 Mars 2020.

26. Mehra, M.R., et al., *Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis.* Lancet, 2020.
27. CREDIBLEMEDS: QT drugs lists https://www.crediblemeds.org/healthcare-providers/ .Accessed Mars 2020
28. Han, C., et al., *Digestive Symptoms in COVID-19 Patients With Mild Disease Severity: Clinical Presentation, Stool Viral RNA Testing, and Outcomes.* Am J Gastroenterol, 2020.
29. *Base de donnés thériaque:monographie plaquenil 200 mg updating 30 March 2020 .thériaque.org. accessed April 2020*
30. Rossi, M. and G. Giorgi, *Domperidone and long QT syndrome.* Curr Drug Saf, 2010. **5**(3): p. 257-62.
31. *Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19.* Ameican College of Cardiology, Mar 29, 2020.
32. Ying, W., Y. Qian, and Z. Kun, *Drugs supply and pharmaceutical care management practices at a designated hospital during the COVID-19 epidemic.* Res Social Adm Pharm, 2020.
33. Gross, A.E., et al., *The Effect of a Piperacillin/Tazobactam Shortage on Antimicrobial Prescribing and Clostridium difficile Risk in 88 US Medical Centers.* Clin Infect Dis, 2017. **65**(4): p. 613-618.

