Adverse Drug Reactions of Potential Antiviral Drugs under Evaluation for the Treatment of COVID-19: Analysis of WHO Global Pharmacovigilance Database

[1*]Sangam Subedi,[2]Nim Bahadur Dangi and [3]Aashish Bhattarai.

1. Kantipur Institute of Health Sciences and Kantipur Dental Hospital, Pokhara, Nepal
2. School of Health and Allied Sciences, Pokhara University, Nepal
3. School of Medical Sciences, Banasthali, Kathmandu, Nepal

ABSTRACT

***Background*:** VigiBase database is a world health organization global pharmacovigiliance database of spontaneous reported adverse drug reaction (ADR).There is no standard treatment so far, against Coronavirus disease 2019 (COVID-19). Azithromycin, chloroquine, hydroxychloroquine, lopinavir, ritonavir, and remdesivir are the potential antiviral drugs under evaluation for the treatment of COVID-19. So, this study aimed to assess spontaneously reported ADRs to these drugs being evaluated for treatment of COVID-19.

***Methods*:**This was a retrospective observational study. ADRs reported till 19th August 2020 retrieved from VigiBase Safety Reports .Comparative analysis was done for the ADRs reported for those drugs.

Results: Gastrointestinal disorders, Injury, poisoning and procedural complication, Investigations, and Skin and subcutaneous tissue disorders were mostly reported for azithromycin (20415), lopinavir(237), remdesivir(1058) and chloroquine (1923) respectively . General disorders and administrative site conditions were mostly reported for hydroxychloroquine (10640) and ritonavir (3348). ADRs reported vary with sex, age group and geographical loactionamong those drugs. Reporting rates were found to decline from 2016 to 2018 in case of Azithromycin and chloroquine whereas reporting rates was found to increase in case of hydroxychloroqine.

Conclusion: Health professionals shall report ADRs observed in the clinical practice and be informed about the reported ADRs through the WHO Global Database.

Keywords: Adverse drug reaction, Pharmacovigilance, Potential Antiviral Drugs, COVID-19, VigiBase

1. INTRODUCTION

Adverse drug reaction (ADR) is a response to a drug which is noxious and unintended. This response occurs at normal doses being used for prophylaxis, diagnosis, or therapy of disease or modification of physiological function [1].World Health Organization collaborating centre for International Drug Monitoring, Uppsala Monitoring Centre (WHO-UMC) maintains the VigiBase database, WHO Global Pharmacovigilance Database of spontaneous reported ADRs. Suspected ADRs of drugs from regional centers are reported to national centers for reporting ADRs of 110 different countries. National centers forward those reported ADRs to WHO-UMC. VigiMatch is an automatic algorithm which is used in VigiBase to detect and remove suspected duplicate reports from the dataset but 'false positives' and 'false negatives' that have been marked and not highlighted by the algorithm respectively may be removed or added in the databases [2,3]. Coronavirus Disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4] COVID-19 was characterized as a pandemic by WHO on 11 March, 2020 [5]. This disease has inflicted insurmountable damage to human lives. As of August 16, 2020, 21.2 million confirmed COVID-19 cases including 76100 deaths from 216 countries were reported to WHO in total [6]. Despite the worsening trends of COVID-19, there has been so far now, no definite treatment against COVID-19. Global efforts are underway for treatment options of COVID-19. The search for COVID-19 therapy is racing against the time and drug repurposing tsunami is on the way[7,8]. Azithromycin, Chloroquine, Hydroxychloroquine, Lopinavir, Ritonavir, and Remdesivir are the potential antiviral drugs under evaluation for the treatment of COVID-19 according to the treatment guidelines of National Institutes of Health (NIH) [9]. Various studies are registered in clinicalTrials.gov registry regarding azithromycin (108 trials), chloroquine (83 trials), hydroxychloroquine (248 trials), lopinavir (82 trials), ritonavir (86 trials) and remdesivir (47 trials) [10]. Azithromycin is indicated for mycobacterial and sexually transmitted infections, chloroquine is indicated for malaria, and extraintestinalamebiasis, hydroxychloroquine is indicated

* Corresponding author: Email:subedisangam@gmail.com, Phone:009779846049344

for lupus erythematosus,malaria and rheumatoid arthritis and combination of lopinavir and ritonavir is indicated for human immunodeficiency virus infections. These are all the Food and Drug Administration (FDA), United States approved indications.Remdesivir is an investigational antiviral drug for the treatment of COVID-19 that has obtained emergency use authorization on May 1, 2020 [11]. The involvement of these drugs among potential antiviral drugs under evaluation increases the use of these drugs. Higher the use of drugs, higher will be the reports sent to UMC. This study aims to assess the ADRs of potential antiviral drugs under evaluation of treatment of COVID-19 (azithromycin, chloroquine, hydroxychloroquine, lopinavir, ritonavir, and remdesivir) reported to WHO Global Database, to find the gender, age group and geographical region where the ADRs were observed in most and the trends of ADRs for last five years.A retrospective observational study was performed to assess adverse drug reactions reported for azithromycin, chloroquine, hydroxychloroquine, lopinavir, ritonavir, and remdesivir till 19th August 2020. ADRs were retrieved from VigiBase Safety Reports (http://www.vigiaccess.org/) [2]. VigiAccess is a user friendly web application that allows the public to access VigiBase. The ADRs reported from different parts of the world were observed through VigiBase. Comparative analysis was done for the ADRs reported, sex distribution, age –group distribution, geographical distribution and the pattern of ADRs for last five years for azithromycin, chloroquine, hydroxychloroquine, lopinavir, ritonavir and remdesivir.

2. MATERIALS AND METHODS

2.1 Materials

ADRs were retrieved from VigiBase Safety Reports (http://www.vigiaccess.org/) [2]. VigiAccess is a user friendly web application that allows the public to access VigiBase.

2.2 Methods

A retrospective observational study was performed to assess adverse drug reactions reported for azithromycin, chloroquine, hydroxychloroquine, lopinavir, ritonavir, and remdesivir upto19th August 2020. The ADRs reported from different parts of the world were observed through VigiBase. Comparative analysis was done for the ADRs reported, sex distribution, age –group distribution, geographical distribution and the pattern of ADRs for last five years for azithromycin, chloroquine, hydroxychloroquine, lopinavir, ritonavir and remdesivir.

2.3 Statistical Analysis

Simple descriptive analysis was performed to compare the number of ADRs reported for each drugs.

3.0 RESULTS

Various ADRs were reported for potential antiviral drugs being evaluated for COVID-19. Gastrointestinal disorders were mostly reported for azithromycin (20415). General disorders and administrative site conditions were mostly reported for hydroxychloroquine (10640) and ritonavir (3348). Injury, poisoning and procedural complications and investigations were mostly reported for lopinavir (237) and remdesivir (1058) respectively. Skin and subcutaneous tissue disorders were mostly reported for chloroquine (1923). Gastrointestinal disorders were reported for chloroquine (1856), lopinavir (184), and ritonavir (2792) in higher numbers. Similarly, skin and subcutaneous tissue disorders were reported in higher numbers for azithromycin (14967) and hydroxychloroquine (6092). Gastrointestinal disorders, as well as cardiovascular disorders, can be problems in the case of a combination of hydroxychloroquine plus azithromycin (Table 1).ADRs reported were more in females among azithromycin, chloroquine and hydroxychloroquine whereas were more in males in lopinavir, ritonavir, and remdesivir. Maximum ADRs reported were of age group 18 to 44 years in case of azithromycin,chloroquine, lopinavir, and ritonavir whereas in case of hydroxychloroquine and remdesivir, ADRs reported were maximum from the age group 45-64 years. Majority of reported ADRs were more from the USA in case of hydroxychloroquine, lopinavir, ritonavir, and remdesivir whereas ADRs reported were maximum from Asia and Europe in case of Azithromycin and Chloroquine respectively. The cardiac disorders associated with chloroquine and hydroxychloroquine are seen to be significant to warn patients. (Table 2).The pattern of ADRs varies among drugs. Reporting rates declined from 2016 to 2018 but rose in 2019 in azithromycin. There was a decline from 2016 to 2018 in reporting of ADRs in the case of chloroquine whereas the numbers of reports were equal in 2018 and 2019. The number of reports rose from 2016 to 2018 whereas there was a decrease in reports of hydroxychloroquine in 2019. ADRs reported an increase in 2017 in comparison to 2016 whereas declined in 2018 and 2019 in the case of both lopinavir and ritonavir. The pattern of ADRs reported yet to be observed in case of Remdesivir (Table 3)

Table 1: Adverse Drug Reactions Reported

ADRs Reported	Azithromycin	Chloroquine	Hydroxychloroquine	Lopinavir	Ritonavir	Remdesivir
Blood and lymphatic system disorders	1094	397	1380	30	725	50
Cardiac disorders	3687	482	1349	35	724	235
Congenital, familial and genetic disorders	121	53	174	26	685	1
Ear and labyrinth disorders	1754	279	499	4	83	3
Endocrine disorders	53	12	85	12	521	3
Eye disorders	1877	760	2255	22	282	14
Gastrointestinal disorders	20415	1856	5013	184	2792	99
General disorders and administration site conditions	13611	775	10640	173	3348	385
Hepatobiliary disorders	1594	161	740	58	1325	64
Immune system disorders	5555	164	1781	28	387	13
Infections and infestations	3090	138	2118	113	1560	149
Injury, poisoning and procedural complications	3086	254	2915	237	2369	221
Investigations	3464	381	3079	101	2222	1058
Metabolism and nutrition disorders	1180	493	762	105	1612	62
Musculoskeletal and connective tissue disorders	1949	465	3500	44	909	17
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	148	23	461	14	314	0
Nervous system disorders	7411	1580	3004	63	1817	88
Pregnancy, puerperiumand perinatal conditions	321	22	282	176	1348	3
Product issues	706	6	316	0	35	13
Psychiatric disorders	2268	662	1185	25	699	39
Renal and urinary disorders	999	104	515	39	1230	364
Reproductive system and breast disorders	307	52	161	11	214	2
Respiratory, thoracic and mediastinal disorders	4631	269	1525	25	663	256
Skin and subcutaneous tissue disorders	14967	1923	6092	81	1974	68
Social circumstances	122	17	364	3	57	25
Surgical and medical procedures	164	20	295	10	300	207

Table 2: Comparisons among preponderance of Sex, Age-group most prevalent and Geography mostly reported

Drugs	Sex distribution	Age-group	Geographical Distribution
Azithromycin	Female	18-44	Asia
Chloroquine	Female	18-44	Europe
Hydroxychloroquine	Female	45-64	Americas
Lopinavir	Male	18-44	Americas
Ritonavir	Male	18-44	Americas
Remdesivir	Male	45-64	Americas

Table 3: ADR reported per year for last five years

Drugs (Total number of ADR reported)	Year	ADR reported
Azithromycin (60334)	2020	5576
	2019	7557
	2018	5319
	2017	5636
	2016	5731
Chloroquine (6556)	2020	973
	2019	278
	2018	278
	2017	306
	2016	339
Hydroxychloroquine (26688)	2020	4715
	2019	4192
	2018	4973
	2017	2529
	2016	2333
Lopinavir (826)	2020	43
	2019	34
	2018	134
	2017	221
	2016	57
Ritonavir (15462)	2020	416
	2019	830
	2018	850
	2017	1223
	2016	1019
Remdesivir (2070)	2020	2070
	2019	-
	2018	-
	2017	-
	2016	-

4. DISCUSSION

This study is one of the few studies highlighting the ADRs of drugs being evaluated for COVID-19. These drugs are also being used for otherpurposes in clinical settings. Azithromycin has the most frequent adverse drug reactions related to the gastrointestinal (GI) tract (e.g. nausea, vomiting, diarrhea, or abdominal pain) [12] that resembles the finding of this study where GI disorders were most observed ADRs for azithromycin. Azithromycin and hydroxychloroquine are found to be associated with QT prolongation in few cases even though the incidence is unknown; their combination may be dangerous [13]. Since the combination of azithromycin and hydroxychloroquine likely to cause GI disorders as well as cardiovascular disorders, NIH panel recommended against the use of combination except for clinical trials (NIH guideline) [9]. Even if the reported cases for hydroxychloroquine and chloroquine were less for cardiac disorders, the numbers are significant. FDA has recommended the cautious use of hydroxychloroquine or chloroquine due to the possibility of heart rhythm problems [14]. The most common ADRs in the remdesivir treated patients were hypoalbuminaemia, hypokalaemia, anaemia, thrombocytopenia, and increased total bilirubin [15]. These adverse events 'investigations' resemble our results where 'investigations' were the adverse drug reactions of

remdesivir reported. ADRs reports for azithromycin, hydroxychloroquine and chloroquine were observed to be more in females, and reports were more in males in the case of lopinavir, ritonavir, and remdesivir. The difference observed in sex group may be due to underreporting among one sex group to others in reporting to the ADRs of drugs [16]. The prevalence of ADRs increases with age [17] whereas our finding showed that ADRs of 4 drugs out of 6, were reported for 18 - 44 years resembling to a study conducted in China [17]. The reports were obtained mostly from the Americans as was observed in the study of Watson et al., 2019[18]. The numbers of reports for the last five years were found to rise and fall for all drugs except remdesivir. The differences in reporting of particular ADRs across drugs cannot be considered to reflect a true difference in ADRs [19]. For remdesivir, just approved for emergency use, the reports for the next four years can be observed if it follows the Weber effect. This effect refers to a pattern of adverse drug reactions reporting with an increase for the first two years after a new drug is marketed, booming in the second year and then declining [20]. Increasing awareness will increase the rate of reporting for years.

5. CONCLUSION

Treatment options for the COVID-19 crisis are being investigated and various strategies of drug repurposing are going on. Reporting ADRs of drug therapy to regional pharmacovigilance centers reaches national centers. These centers forward the ADRs to Uppsala Monitoring Centre (UMC). Through VigiBase, maintained by UMC, various ADRs reported can be assessed. So, health professionals on frontline shall report the ADRs observed in the clinical practice and be informed about the reported ADRs through the WHO Global Database.

Acknowledgement

The authors wish to thank Kantipur Institute of Health Science and Kantipur Dental Hospital, Pokhara-8, Gandaki , Nepal and Pokhara University, Pokhara-30, Gandaki, Nepal.

Conflict of interest

No conflict of interest.

Contributions of Authors

Subedi S conceived the research. Manuscript was written by Subedi S and Bhattarai A. They performed the data analysis as well. The other author, Dangi NB reviewed and approved the submitted manuscript. The paper was finalized and submitted by Subedi S.

6. REFERENCES

[1] World Health Organization. International drug monitoring: the role of national centers. Geneva: World Health Organization; 1972. 48p. Report No.:498.

[2] World Health Organization. Vigiaccess [Internet]. Uppsala, Sweden: Uppsala Monitoring Centre; 2015 [cited 2020 Aug 19]. Available from: http://www.vigiaccess.org/.

[3] Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. Drug Information Journal. 2008 Sep;42(5):409-19.

[4] World Health Organization [Internet]. Geneva, World Health Organization; 2020. Naming the coronavirus disease (COVID-19) and the virus that causes it; 2020 [cited 2020 Aug 15]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.

[5] World Health Organization. Coronavirus disease 2019 (COVID-19): situation report. Geneva: World Health organization, 2020. 9p. Report No.: 51.

[6] World Health Organization. Coronavirus disease 2019 (COVID-19): situation report. Geneva: World Health Organization, 2020. 16p. Report No.: 209.

[7] Aljofan M, Gaipov A. COVID-19 Treatment: The Race Against Time. Electron J Gen Med. 2020;17(6):em227.

[8] Mucke HAM. COVID-19 and the Drug Repurposing Tsunami. Assay Drug Dev Technol. 2020;18(5):211-214.

[9] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health; 2020 [cited 2020 Aug 23].Available from: https://www.covid19treatmentguidelines.nih.gov/whats-new/.

[10] US National Library of Medicine [Internet]. Bethesda, MD; 2020. ClinicalTrials.gov; 2020[cited 2020 Aug 24].Available from: www.clinicaltrials.gov.

[11] Aschenbrenner DS. Remdesivir Receives Emergency Use Authorization for Severely Ill Patients with COVID-19. AJN The American Journal of Nursing. 2020 Jul 1;120(7):26.

[12] Bleyzac N, Goutelle S, Bourguignon L, Tod M. Azithromycin for COVID-19: More Than Just an Antimicrobial?.Clin Drug Investig. 2020;40(8):683–6.

[13] Chorin E, Dai M, Shulman E, Wadhwani L, Bar-Cohen R, Barbhaiya C, Aizer A, Holmes D, Bernstein S, Spinelli M, Park DS. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nature Medicine. 2020 Apr 24:1-2.

[14] Food and Drug Administration [Internet]. United States: United States Government; 2020. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems; 2020 Jan 07 [cited 2020 Aug 24]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

[15] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet. 2020 May;395(10236):1569-78.

[16] Watson S, Caster O, Rochon PA, den Ruijter H. Reported adverse drug reactions in women and men: aggregated evidence from globally collected individual case reports during half a century. EClinicalMedicine. 2019 Dec 1; 17:100188.

[17] Sikdar KC, Alaghehbandan R, MacDonald D, Barrett B, Collins KD, Donnan J, Gadag V. Adverse drug events in adult patients leading to emergency department visits. Annals of Pharmacotherapy. 2010 Apr;44(4):641-9.

[18] Wei RL, Xie YM, Zhang WL. Analysis on 1500 adverse reactions of GuizhiFuling Capsules based on spontaneous response system. ZhongguoZhongyaozazhi= Zhongguozhongyaozazhi= China journal of Chinese material medica. 2019 Apr 1;44(7):1497-502.

[19] Chhabra P, Chen X, Weiss SR. Adverse event reporting patterns of newly approved drugs in the USA in 2006: an analysis of FDA Adverse Event Reporting System data. Drug safety. 2013 Nov 1;36(11):1117-23.

[20] Weber JCP. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs. In: Rainaford KD, Velo GP, editors. Side-effects of anti-inflammatory drugs, advances in inflammation research. New York: Raven Press; 1984. P. 1-7