Descriptive analysis of COVID19-related spontaneous reports from VigiBase: interim results

Report from the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC)

Descriptive analysis of COVID19-related spontaneous reports from VigiBase: interim results (2020-04-19)

The UMC is engaged in sharing relevant aggregated data on ADR reporting within the PIDM network on drugs used in the treatment of covid-19 disease. The present analysis primarily focuses on drugs included in the WHO Solidarity trial. Future reviews will include additional agents that are currently being investigated in clinical trials reported in the WHO International Clinical Trials Registry Platform.

This is the third report from UMC, to accompany the weekly regulatory updates from WHO. As before, this report is mainly descriptive in nature. Systematic signal detection or causality assessment has not yet been carried out performed as the signs and symptoms of the disease are still only partly described. Drugs in these reports to VigiBase are, in most cases, approved drugs (for other indications); remdesivir on the other hand, has neither an established, publicly available safety profile nor a proven positive benefit-harm balance for any indication yet.

Reports for the drugs are presented below with general characteristics and statistics accessible in separate tables for an easy overview.

Reports in VigiBase

The methodology of search has been refined for this third review. Reports extracted include those that were identified by an indication field mapped to the PT MedDRA-term “coronavirus infection” or by free-text terms (coronavirus, Wuhan coronavirus, COVID). Reports were received at the National Centres between 1 January and 19 April 2020 and were reported to VigiBase no later than 19 April 2020.[1]

When retrieving and reviewing relevant ADR reports, it was noted that there were several reports without a specific, Covid-treatment related ADR. For example, there were reports that had no ADR but simply noted details such as ‘successful off-label use without ADR’, or, Corona virus as concurrent medical history with or without ADR for other drugs, or referred to ‘corona testing’, or mentioned avoiding drugs with the hope of reducing the risk of developing covid-19 disease.

Summary

Vigibase continues to receive Individual case safety reports for drugs used in the treatment of Covid-19. Most reports continue to come from the European Region, but geographical spread continues to

[1] If the arrival date at the National Center was not reported, the date of latest update at the National Center was used instead.in

increase as the first reports from the Western Mediterranean region are noted in this weekly review. The most commonly reported ADRs continue to be those included in available product labelling. Overall, QT prolongation and hepatic events are the most commonly reported serious events. Renal events and skin events, including one case of toxic epidermal necrolysis, have also been reported and are further described in this review.

Characteristics of the reports

A total of 182 new case reports were identified by the selected search strategy (Table 1).

Cumulatively, there are now a total of 456 reports from 4 WHO regions with the large majority of reports from the European region (87.7%). 66% of the reports were classified as "serious" (Table 2), with 68% of the reports involving males and 29% females. Most of the reports included at least one of the drugs that are being investigated in the SOLIDARITY trial; the drug was described either as "suspected'' or ''interacting". The search also identified a small number of additional reports describing other drugs that are being used in the treatment of COVID-19 disease.

Characteristics of the reports for drugs included in the WHO Solidarity trial

Hydroxychloroquine alone or in combination with azithromycin

There were 127 new reports for this time-period and subcategory, of which 92 were for men, 33 for women and two of unknown sex.

The reports were shared from the European region (104), Region of the Americas (22), Western Pacific region (1) and Eastern Mediterranean region (1).

There were 22 reports in the age group 18-44 years, 51 reports in the age group 45-64 years, 29 reports in the age group of 65-74 years, 21 reports in the age group of 75 years and above, and four reports of unknown age.

Azithromycin was co-reported in 51 reports, of which it was marked as co-suspected or interacting in 46 reports and as concomitant in five reports.

Adverse events

Most frequently reported adverse drug reactions were heart rhythm disorders and hepatitis. QT-prolongation, which is the most commonly reported ADR among the reports (36 reports of which 32 were serious), is listed only under the section "Overdose" in the product label for the drug.[1] Under hepatobiliary disorders in the label, abnormal liver function tests is listed as "Uncommon". Hepatitis is however not listed (there were 19 reports of hepatitis (16 serious) and 7seven of hepatitis acute (all serious).[1] Azithromycin, for which hepatitis is listed, was however co-reported on several of the reports.

Toxic epidermal necrolysis

There was one report of Toxic Epidermal Necrolysis (TEN) which is a serious skin reaction often caused by drugs. It was co-reported and co-suspected for the drugs paracetamol and ceftriaxone which were all used during the same time-range of 23 days, with a time to the onset of the reaction of 19 days. The product label for hydroxychloroquine mentions toxic epidermal necrolysis with a "Frequency not known".[1] For paracetamol it is listed as: "Very rare: skin reactions"[2] and for ceftriaxone it is listed as "Frequency not known".[3]

Chloroquine

There were 32 reports in this subcategory of which 16 were for men, 15 for women and one of unknown sex.

The reports were shared from the European Region (17), Western Pacific Region (11 reports), Region of the Americas (2), Eastern Mediterranean Region (1),

There were two reports in the age group 18-44 years, 17 reports in the age group 45-64 years, six reports in the age group 65-74 years, four reports in the age group of 75 years and above, and three reports of unknown age.

Adverse events

The most frequently reported MedDRA Preferred Term was Electrocardiogram QT prolonged, which was the most prevalent in the 24 serious reports, featuring in 18 of those.

There was one report of a suspected potentiating interaction between chloroquine, lithium and quetiapine in a patient affected by bipolar disorder type 2. Chloroquine is known to reduce the excretion rate of lithium.

Finally, there was one fatal report, which included the PT "Methaemoglobinaemia". It describes a 57-year old man treated with 500mg of chloroquine for one day for coronavirus infection, increased to a total of 1500 mg the day after. The dose was progressively decreased to 1000mg, 500mg and 250mg over the following four days. The patient was also treated with concomitant tocilizumab, though no dates of treatment were available for either drug. This adverse effect is known for antimalarials, except chloroquine; there are a few published case reports of chloroquine-induced methaemoglobinaemia.[4-7]

Lopinavir;ritonavir

During this reporting period 49 new reports in which lopinavir/ritonavir were reported as suspecting or interacting drugs were reviewed. These concerned 35 male and 12 female patients (2 of unknown sex) between the ages of 22 and 78 years (four reports did not include age). 45 reports originated from the WHO-EURO region and three from the WHO Western Pacific region, and one from WHO Eastern Mediterranean Region

Adverse events

The most commonly reported ADRs were those which are included in the product labelling for lopinavir/ritonavir.[8]

Diarrhoea was included in 12 reports, all but one of which was "nonserious" (two reports had no "seriousness" included).

Hepatobiliary reactions included hepatitis (five reports), hepatocellular injury (four reports), blood bilirubin increased (two reports), cholestasis (tow reports), hyperbilirubinemia (two reports), transaminases increased (two reports), mixed liver injury (two reports), and hepatitis acute (One report). The majority of reports describing hepatobiliary ADRs were "serious". Concomitantly administered drugs considered to be co-suspected and/or interacting were hydroxychloroquine, azithromycin, ceftriaxone, cefotaxime and interferon-beta

Electrocardiogram QT prolonged was included in 11 reports; hydroxychloroquine was reported as a concomitant medication in three of these reports was. One of these cases had a co-reported reaction of cardiac arrest.

In a majority of the reports, lopinavir; ritonavir was reported to have been "withdrawn" and patient outcomes noted to be "recovering"

Remdesivir

During this reporting period, seven new remdesivir reports were shared, one of which where the drug was reported only as a concomitant medicine. These concerned one female and six male patients between the ages of 39 and 81 years (median 48 years) and all originated from the WHO-EURO region. Given the fact that remdesivir is currently not licensed and the numbers of reports remain lower compared to the other drugs used in the Solidarity trial, a cumulative review is provided below.

Adverse events

Hepatobiliary events

Cumulatively, the most common reported suspected reactions from remdesivir are hepatobiliary-related events (SOC Hepatobiliary disorders, SOC Investigations). Such events account for 18 events in total out of the 71 reported events for remdesivir. Two such reports were submitted during this period:

In one case, 'transaminases increased' was co-reported with rash. Concomitant drugs included two antibiotics, antiviral, NSAID, paracetamol, sedative, antithrombotic and oxygen. After five days, remdesivir was withdrawn due to increased transaminases, which then subsided. Remdesivir was later re-introduced and withdrawn again due to a rash which also resolved.

Another case reported 'pulmonary embolism'' and hepatic enzyme increased' with remdesivir as the only suspect drug. Other drugs that were used concomitantly included hydroxychloroquine, lopinavir/ritonavir, two antibiotics and oral steroids. The time to onset was five days for the pulmonary embolism and eight days for the liver enzyme reaction. Remdesivir was continued for eight days while all other drugs, except one antibiotic, were discontinued between 5-7 days. The reactions were reported as not recovered at the time of reporting.

Renal events

Cumulatively, eight reports of renal events (Renal and urinary disorders SOC, Investigations SOC) have been received, two of which were reported in this period.

One report, with remdesivir being the only reported drug notes renal failure two days after starting remdesivir. The drug was withdrawn, and the outcome of the patient is unknown.

Another report noted acute kidney injury with an unknown time to onset (TTO). Remdesivir was reported as the sole suspect drug, with hydroxychloroquine, lopinavir/ritonavir and tocilizumab among the long list of concomitant drugs. Laboratory data suggested creatinine and urea levels started to increase already before remdesivir initiation. The patient later underwent haemodialysis, and any effect of withdrawal of remdesivir and one antibiotic on creatinine and urea levels is unclear.

Skin events

Cumulatively, seven reports of skin events have been received, three during this period.

Apart from the one already described above (under the heading *Hepatobiliary event*s), a second case describes a rash with a TTO of one day where the drug was not withdrawn, and the reaction did not subside. An extensive list of concomitant drugs including hydroxychloroquine, antibiotics, narcotic sedatives, antithrombotic suggest it was a sedated patient with severe Covid-19 disease. A third case reporting maculopapular rash had a fatal outcome. The suspected drug was cefotaxime (withdrawn), with the indication Klebsiella infection. The rash resolved 10 days before death occurred. Remdesivir was reported as a concomitant drug started three days before the reaction and 15 days before death

occurred. There was no record of what remdesivir treatment was discontinued. Other concomitant drugs in the report were sulfentanyl, propofol, pantoprazole, acetylsalicylic acid, loxapine and enoxaparin, possibly indicating a sedated patient with severe COVID-19 disease. Cause of death is noted as infectious pneumonitis.

In summary, the remdesivir spectrum of ADRs reported thus far seem to be largely within the publicly available information on the drug.[9-13]

Non-solidarity-drug use in covid-19 with relevant ADR reporting in Vigibase

A minority of cases identified in Vigibase with the current search strategy reported using other drugs for the treatment of Covid–19. These include interleukin inhibitors (tocilizumab, siltuximab, anakinra), selective immunosuppressants (the JAK inhibitor baricitinib, the inhibitor of terminal complement eculizumab, and the bradykinin receptor antagonist icatibant), and antivirals (oseltamivir, darunavir alone and in combination with cobicistat, interferon beta). As data accumulate, more detail analysis might be possible in subsequent weekly reports. These are included in Table 3.

Disclaimer

Data in the reports are not complete and only a subset of the reports in this analysis contained narratives. With limited data available at this stage of the pandemic and the uncertainty over other confounders (such as the underlying disease), this report is no more than a preliminary overview of cases and reported ADRs. Manual de-duplication has not been carried out automatically and may require further follow-ups. Any signals detected in the future will be communicated separately.

Errata from report dated 2020-04-12

2020-04-12: Total counts of cases for the drugs or drug groups: Hydroxychloroquine alone or with antibiotics other than azithromycin, Hydroxychloroquine in combination with azithromycin, Azithromycin alone or with other antibiotics, lopinavir; ritonavir and remdesivir, have been revised and some cases have been excluded. For the first drug group, the total of 49 is brought to 46 after the exclusion of three reports (one concerned a patient in prophylactic treatment for COVID-19, two concerned patients negative to test for COVID-19, whether PCR or unspecified). For the second group, the total of 51 should be brought to 50 since the one patient, while positive to COVID-19, experienced propofol infusion syndrome but not suspected adverse effects related to the use of drugs in the SOLIDARITY trial.

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Drug group	N_old	N_new	N_total
AZM	70	48	118
CQ	23	17	40
HCQ	129	127	256
LR	115	54	169
RDV	33	7	40
Other	48	44	92
N unique reports	274	182	456

Table 1. N_old display reports entered in VigiBase no later than the 12th of April. N_new between 13th and 19th of April. AZM = Azithromycin, CQ=Chloroquine, HCQ = Hydroxychloroquine, LR = Fixed dose combination of Lopinavir and Ritonavir, RMD = Remdesivir, Other = Other Drugs, see Appendix. Counts include suspected, interacting and concomitant drugs, as long as at least one of the listed drugs was reported as suspected or interacting in each report. As one report may contain several drugs, rows are not mutually exclusive.

		AZM		CQ		HCQ		LR		RMD		Other		All	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Report characteristics															
	Total N	118	100	40	100	256	100	169	100	40	100	92	100	456	100
	Susp. or Int.	99	83.9	32	80	211	82.4	152	89.9	40	100	69	75	456	100
	Serious	93	78.8	27	67.5	182	71.1	92	54.4	18	45	68	73.9	303	66.4
	Fatal	8	6.8	1	2.5	20	7.8	9	5.3	7	17.5	29	31.5	47	10.3
Sex															
	Male	85	72	21	52.5	186	72.7	113	66.9	35	87.5	66	71.7	311	68.2
	Female	33	28	18	45	65	25.4	53	31.4	5	12.5	22	23.9	132	28.9
	Missing	0	0	1	2.5	5	2	3	1.8	0	0	4	4.3	13	2.9
Age															
	Median (Q1-Q3)	61 (51-68)		60 (54-67)		63 (51-71)		65 (55-73)		58 (44-66)		63 (53-69)		63 (53-71)	
	< 18 years	0	0	0	0	1	0.4	2	1.2	1	2.5	0	0	2	0.4
	18 - 44 years	18	15.3	2	5	38	14.8	14	8.3	9	22.5	15	16.3	58	12.7
	45 - 64 years	52	44.1	21	52.5	97	37.9	61	36.1	16	40	31	33.7	178	39
	65 - 74 years	29	24.6	7	17.5	59	23	42	24.9	10	25	24	26.1	109	23.9
	> 74 years	14	11.9	7	17.5	47	18.4	37	21.9	2	5	10	10.9	78	17.1
	Missing	5	4.2	3	7.5	14	5.5	13	7.7	2	5	12	13	31	6.8
WHO region															
	African Region	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Eastern Mediterranean Region	2	1.7	1	2.5	1	0.4	1	0.6	0	0	1	1.1	2	0.4
	European Region	106	89.8	25	62.5	228	89.1	161	95.3	40	100	78	84.8	400	87.7
	Region of the Americas	8	6.8	3	7.5	26	10.2	3	1.8	0	0	7	7.6	33	7.2
	South-East Asia Region	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Western Pacific Region	2	1.7	11	27.5	1	0.4	4	2.4	0	0	6	6.5	21	4.6

Table 2. AZM = Azithromycin, CQ=Chloroquine, HCQ = Hydroxychloroquine, LR = Fixed dose combination of Lopinavir and Ritonavir, RMD = Remdesivir, Other = Other drugs, see Appendix. Susp. or Int. = Drug was reported as suspected or interacting, Q1-Q3 = First to third quartile. Counts include suspected, interacting and concomitant drugs, as long as at least one of the listed drugs was reported as suspected or interacting in each report. As one report may contain several drugs, columns are not mutually exclusive.

Drug	N	%
Total	92	100
Tocilizumab	51	55.4
Oseltamivir	13	14.1
Darunavir	8	8.7
Ritonavir	8	8.7
Baricitinib	6	6.5
Cobicistat;Darunavir	4	4.3
Anakinra	3	3.3
Interferon beta	3	3.3
Interferon beta-1a	3	3.3
Siltuximab	3	3.3
Eculizumab	1	1.1
Icatibant	1	1.1
Umifenovir	1	1.1

Table 3. Drugs included in the Other drugs-category. Counts include suspected, interacting and concomitant drugs, if at least one of the drugs described in this report was reported as suspected or interacting in each report. As one report may contain several drugs, rows are not mutually exclusive. Total is the total number of unique reports.

CAVEAT DOCUMENT

2018-11-20

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

i. recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information
ii. explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases
iii. affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.