Descriptive analysis of COVID-19-related spontaneous reports from VigiBase: interim results

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

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Summary

This fourth report is still mainly descriptive in nature and is dominated by the reporting on drugs in the WHO SOLIDARITY trial. Systematic signal detection and causality assessment have not been performed for COVID-19 reports at the current time. Drugs, where reactions have been reported into VigiBase (the WHO global database of Individual Case Safety Reports), are, in most cases, approved (for other indications) while remdesivir, prior to COVID-19, had been investigated but not licensed for use in Ebola disease. Clinical trials are being performed and communicated elsewhere for the drugs. Reports for the drugs are presented below with general characteristics and statistics accessible in separate tables for an easy overview. Reports have now been shared from five of the six WHO regions, with the largest number still originating from the WHO European Region. The most commonly reported adverse drug reactions (ADRs) continue to be those included in available product labelling or information; QT prolongation and hepatic events are the most commonly reported events.

Reports in VigiBase

The methodology of search has been refined for this fourth review. Reports are screened for drugs given on the indication “Corona virus infection”, by relevant free-text terms and relevant laboratory tests. The last two were reviewed manually before inclusion. Reports were received at the National Centres between 1st January and 3rd May 2020 and were reported to VigiBase no later than 3rd May 2020.[1] Reports were included when they reported suspected/interacting drugs included in the SOLIDARITY trial, or in a list based on medical-expertise and indicated for Corona virus infection. See Table 3.

When retrieving and reviewing relevant ADR reports for this analysis, reports without specific COVID-19 treatment-related ADRs have been observed. Examples were: treatment response or non-response in off-label use without other ADRs, corona virus reported as concurrent medical history with or without ADR for other drugs, corona virus test reported and treatment non-compliance in the hopes of reducing the risk of developing COVID-19 disease. We saw traces that the pandemic indirectly affected health care also in non-COVID-19 positive patients and drug use patterns.

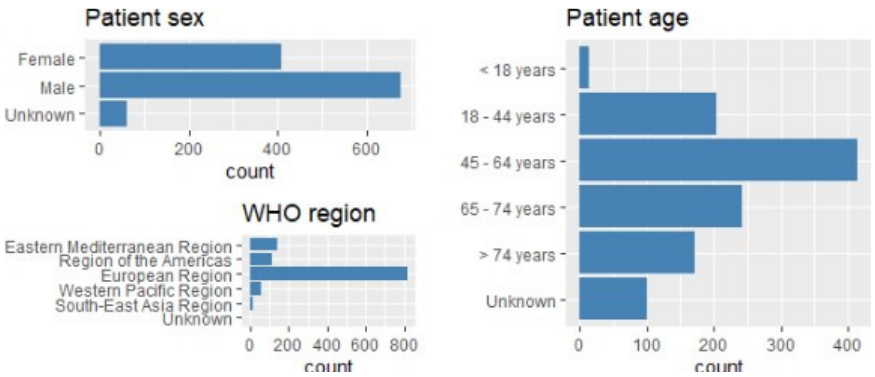
[1] If the arrival date at the National Centre was not reported, the date of latest update at the National Centre was used instead.

Characteristics of the reports

Since the last analysis (summarised in WHO Regulatory Update No. 7), 686 new case reports have been identified using the selected search strategy (Table 1). These new cases were reported to Vigibase between 20th April and 3rd May 2020. Cumulatively, there has been a total of 1146 reports from five WHO regions with the large majority from the European region (71.5 %). 57.7 % of the reports were classified as "serious" (Table 2) but not all reporting standards include seriousness (e.g. INTDIS). Males accounted for 59% of the reports and females 36%.

Most of the reports described at least one drug or substance in the WHO Solidarity trial (i.e. hydroxychloroquine, chloroquine, azithromycin, the combination lopinavir;ritonavir and remdesivir) reported as either suspected or interacting. The search also identified a smaller number of additional reports describing other drugs known to be used in the treatment of COVID-19 disease. Tocilizumab was the most reported (>100 reports) among these drugs and was included in the analysis. Overall reporting demographics are shown in Figure 1. In line with males being more affected by COVID-19 infection globally, for all drugs except chloroquine, the reporting was most prevalent for males. Patient ages were similar between drugs, although lopinavir;ritonavir had the highest median age.

A)



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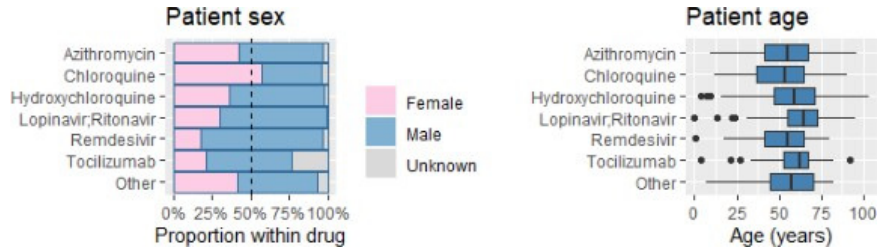

Figure 1. Overall demographics of case safety reports sent into VigiBase in treatment of COVID-19. A) All reports. B) Reports by drug. The B) graphs rely on counts of reports which include each drug as suspected or interacting. Reports including several drugs will be counted once for each reported drug. Patient age boxes show medians and interquartile ranges.

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

Hydroxychloroquine alone or in combination with azithromycin

There were 360 new reports for hydroxychloroquine during this time period, adding to a cumulative total of 570 reports. The new reports included 206 men, 144 women and 10 with unknown sex.

The new reports were shared from the European region (253), Region of the Americas (50), Eastern Mediterranean region (36), South East Asia (13) and Western Pacific region (8).

In the new reports there were 75 reports in the age group 18-44 years, 132 reports in the age group 45-64 years, 68 reports in the age group 65-74 years, 59 reports in the age group 75 years and above and 21 reports of unknown age.

For the new reports, hydroxychloroquine was a single suspected drug in 177 cases.

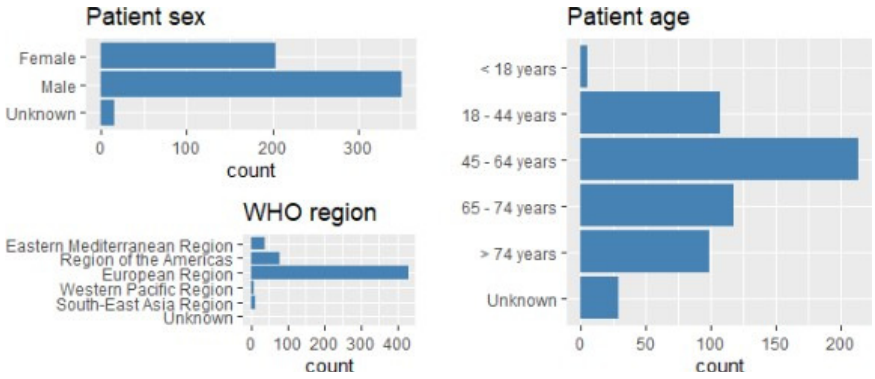

Figure 2. Demography of VigiBase reports received cumulatively so far on hydroxychloroquine as suspected or interacting drug.

Adverse events

The most frequent reported adverse drug reactions included nausea, diarrhoea, vomiting which are all labelled for hydroxychloroquine.[1] QT-prolongation which still is the most commonly reported ADR among the newest reports (111 new reports of which 93 serious), is listed only under the section "Overdose" in the product label for the drug.[1] Reports that included doses up to 1000 mg, which exceeds what is the recommended dose for the drug per day, were identified. Among the new QT-prolongation reported cases, there were reports with a maximum recommended dose, which indicates that the ADR may occur even within approved drug doses. The risk for developing the ADR from the drug was also seen in patients with specific risk factors including renal and/or hepatic disease, advanced age and bradycardia, the latter three being common features in COVID-19 diseases. Hepatitis was another ADR that had a 100% increase (23 new cases, all serious), submitted from a single European country.

Under hepatobiliary disorders in the label for hydroxychloroquine, abnormal liver function tests are listed as "Uncommon" while hepatitis is not.[1] However, co-reported drugs as azithromycin, tocilizumab and lopinavir;ritonavir, for which hepatitis is listed, were included in 20 of the 23 reports.

Toxic epidermal necrolysis

Although one case of Toxic Epidermal Necrolysis (TEN) was reported during the previous period, there were no new reports of the ADR during this period.

Chloroquine alone or in combination with azithromycin

There were 143 reports in this subcategory of which 52 were for men, 85 for women and 6 of unknown sex. Of these, 111 were reported in combination with azithromycin either as suspected/interacting or concomitant.

The reports came from countries in the Eastern Mediterranean Region (104), European Region (25), Western Pacific Region (11) and South East Asia Region (3).

There were four reports in the age group below 18 years, 52 reports in the age group 18-44 years, 44 reports in the age group 45-64 years, 26 reports in the age group 65-74 years, six reports in the age group 75 years and above, and 11 reports of unknown age.

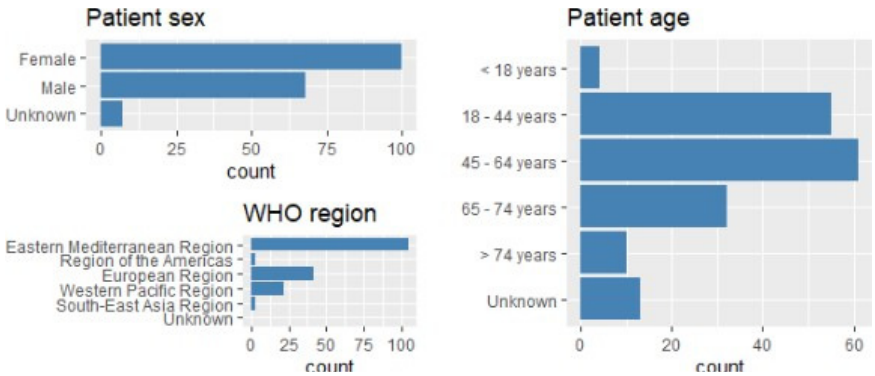

Figure 3. Demographics of VigiBase reports received cumulatively so far for chloroquine as suspected or interacting drug.

Adverse events

The most frequently reported MedDRA Preferred Terms (>10 reports) were: vomiting (35 reports), followed by nausea (33 reports), diarrhoea (25 reports), insomnia (25 reports), abdominal pain upper (21 reports), vision blurred (15 reports), electrocardiogram QT prolonged (13 reports), vertigo (13 reports).

Of the 39 serious reports, a minimum of two reports included at least one of the following Preferred Terms: Electrocardiogram QT prolonged (13 reports), Hallucination (7 reports), insomnia (6 reports), vomiting (5 reports), dizziness (4 reports), nausea (4 reports), abdominal pain upper (3 reports), palpitations (2 reports), vertigo (2 reports), acute kidney injury (2 reports).

Azithromycin

Reports including azithromycin are described in the sections of chloroquine, hydroxychloroquine or lopinavir;ritonavir. There was only one report with azithromycin alone, used to treat COVID-19. It described a 35-year old male who experienced *Clostridium difficile* colitis. Additional co-suspects or concomitant treatments may have been administered but were not reported.

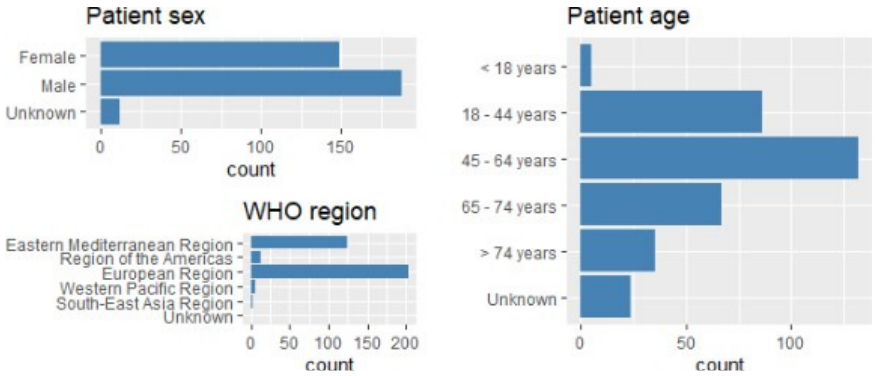

Figure 4. Demography of VigiBase reports received cumulatively so far on azithromycin as suspected or interacting drug.

Lopinavir;ritonavir

During this reporting period 87 new reports, with lopinavir;ritonavir as suspecting or interacting drugs, were reviewed. These concerned 62 male and 25 female patients; median age of patients described in the new reports was 64 years (3 reports had age unreported). 81 reports originated from the WHO European region, five from the WHO Western Pacific region and one Unknown.

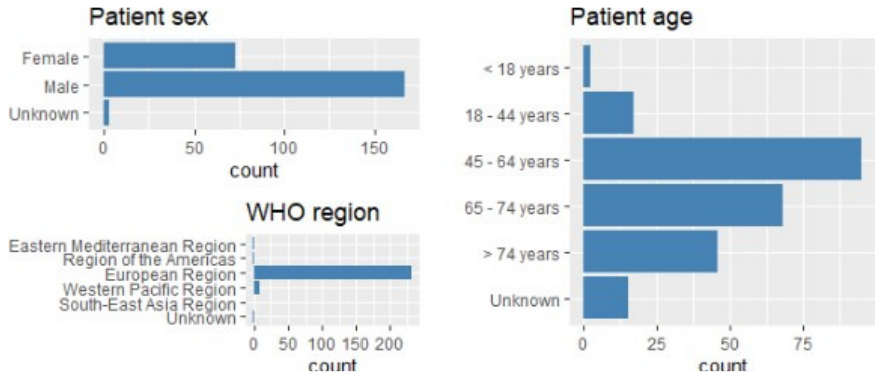

Figure 5. Demographics of VigiBase reports received cumulatively so far for lopinavir;ritonavir as suspected or interacting drug.

Adverse events

The most commonly reported ADRs continued to be those which are included on the product labelling for lopinavir;ritonavir.[2]

Of the most commonly reported ADRs during the reporting period, diarrhoea (14 reports, cumulative 69), hepatocellular injury (14 reports, cumulative 27) and electrocardiogram QT prolonged (6 reports, cumulative 21).

Hypertriglyceridemia was included on a total of seven reports during the reporting period, bringing the cumulative total to 13 (an increase of 117%). One of these cases was complicated by acute pancreatitis. Hyperglyceridaemia and pancreatitis are both included in the product labelling

There were two reports of rhabdomyolysis, bringing the cumulative total to three. Two of the three reports included atorvastatin as a concomitant agent, in spite of a known drug-drug interaction with lopinavir;ritonavir. One case was complicated by renal failure.

During the reporting period there were seven new reports suggestive of renal failure (3 “renal failure”, 3 “acute kidney injury” and 1 “renal impairment”). Included in the product labelling are creatinine clearance decreased, nephritis, haematuria.[2]

New notable reactions during the reporting period were immune thrombocytopenic purpura, acute coronary syndrome, atrial flutter, atrial fibrillation, AV block, pancreatitis acute, peripheral sensory neuropathy.

Remdesivir

There was a total of 56 reports of remdesivir in VigiBase. During this reporting period, 16 new remdesivir reports were shared, in all of which the drug was reported as suspected for the adverse events. These concerned five female and nine male patients as well as two patients of unknown sex between the ages of six months and 69 years, and all originated from the WHO European region. An overview of the cumulative number of reports up until the previous period is available in the previous report.

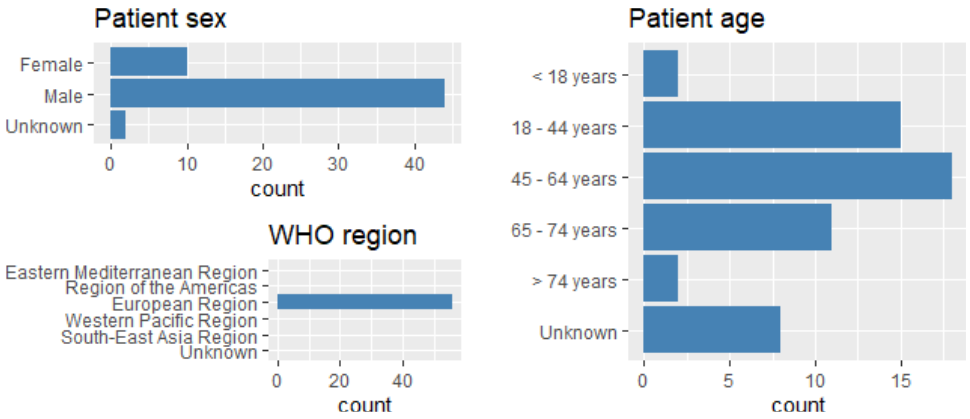

Figure 6. Demography of VigiBase reports received cumulatively so far on remdesivir as suspected or interacting drug.

Adverse events

Hepatobiliary events

As in the previous report, the most commonly reported suspected reactions for remdesivir were, for this period, hepatobiliary-related events (SOC Hepatobiliary disorders, SOC Investigations). There were six reports with hepatic reactions submitted during this period.

One case reported hepatic function abnormal with a time-to-onset of two days. The drug was withdrawn, the patient had not recovered at the time of the report. The second case reported “hypertransaminasaemia” with a time-to-onset of two days. Rash was co-reported and occurred after one day of treatment. The drug was withdrawn, the patient had not recovered at the time of the report. The third case reported “hypertransaminasaemia” with a time-to-onset of three days. The drug was withdrawn and the patient did not recover. The fourth case reported alanine aminotransferase abnormal with a time-to-onset of one day. Concomitant use of piperacillin/tazobactam was reported, which is associated with hepatic events and provides a possible alternative aetiology of the event. The fifth case reported hepatotoxicity with a time- to-onset of six days. The drug was withdrawn, and outcome reported as “Not recovered”. The sixth case reported “alanine aminotransferase increased” and “aspartate aminotransferase increased” with a time-to-onset of the reactions at nine and 10 days respectively. The drug was withdrawn and the patient had not recovered from the increased liver enzymes at the time of the report.

Renal events

Cumulatively, 10 reports of renal events (Renal and urinary disorders SOC, Investigations SOC) have been reported, of which one report of remdesivir being the only suspected drug notes renal failure one day after starting remdesivir. An extensive list of concomitant drugs including among others hydroxychloroquine, azithromycin and lopinavir;ritonavir, all known to have been used in the treatment of COVID-19 disease. The drug was not withdrawn and the patient's outcome was death. The other report noted acute kidney injury with a time-to-onset of three days. Action taken with the drug was unknown but it was recorded that the patient had recovered.

Skin events

Cumulatively, 10 reports of skin events have been reported, three during this period, all with the MedDRA Preferred Term "Rash".

Including the report already described above (under the heading "Hepatobiliary events"), all three reports had a time-to-onset of the rash of one day. In the first report, the drug was not withdrawn but the patient was reported to have recovered from the event. In the second report, the drug was withdrawn but the patient had not recovered at the time of the report. In the third case, the drug was withdrawn and then re-started, with unrecorded information about the outcome of both the reactions.

Other events

The other reported adverse events were, in two cases hyperkalaemia with a time-to-onset of one and three days respectively. Both cases had other co-suspected drugs, both had the combination product macrogol 3350;potassium;sodium bicarbonate;sodium chloride with the indication of constipation. Two cases had the reported term "maternal exposure during pregnancy", one reported together with hypotension with a duration of one day and outcome of the hypotension as recovered, one without further information. In none of the cases the outcomes of the pregnancies were recorded. In two other cases diarrhoea was reported, in one it was the sole reported reaction with unknown time-to-onset and in the other it was co-reported with faeces discoloured and pyrexia, and had time-to-onset of one day for diarrhoea and faeces discoloured and three days for the pyrexia. Finally, there was one report of pancreatitis with time-to-onset of two days. The drug was not withdrawn, but he patient recovered.

In summary, the spectrum of ADRs reported for remdesivir thus far appears to be consistent with the limited available information for the drug.

Non-solidarity-drug use for COVID-19 with relevant ADR reporting in VigiBase

A number of cases (identified by the search strategy) are on ADRs with other drugs in the treatment of COVID–19. The drug among these with the greatest number of reports is the interleukin inhibitor tocilizumab, the reporting of which is summarized below.
At the time of this reporting period, ADR reports for the following substances used for COVID-19 having also been identified in VigiBase (see also Table 3) indicating their use in COVID-19:

- interleukin inhibitors (siltuximab, anakinra, canakinumab)
- selective immunosuppressants (the JAK inhibitor baricitinib, the inhibitor of terminal complement eculizumab, and the bradykinin receptor antagonist icatibant)
- antivirals (oseltamivir, darunavir alone and in combination with cobicistat, umifenovir, interferon beta)
- the somatostatin analogue octreotide
- the respiratory stimulant almitrine
- plasma

As ADR data accumulate for other substances used for COVID-19 treatment, the patterns of reported adverse events for these will be described in subsequent reports.

Tocilizumab

This is the first VigiBase review of ADR reporting for tocilizumab in COVID-19 disease. Tocilizumab is a monoclonal antibody against the interleukin-6 receptor. Approved indications are all non-infectious in nature and include rheumatoid arthritis (RA), juvenile RA, giant cell arteritis and, most relevant for its use in COVID-19, cytokine release syndrome (CRS).[3, 4] The drug is predicted to alleviate the inflammatory cytokine storm described in severe COVID-19 disease.[5]

Cumulatively, 118 reports have been shared from 16 countries globally. Reports come from countries in the European region (81), Region of the Americas (27), Western Pacific region (9) and Eastern Mediterranean region (1). The reports concerned 25 females and 65 males, while 28 reports lack information on sex. The age range of the patients was 4-92 years with a median age of 62.
Dosages reported were within the range recommended for CRS. Whether the patients had an established cytokine storm, or, if the treatment was more prophylactic in nature in COVID-19 patients, is, in most reports, unclear. Information on co-reported medication giving indirect information on the severity of disease varied substantially, where, in slightly more than a half of the reports, tocilizumab was the only reported drug, while in one third of reports, co- medication with other drugs indicated for COVID-19 (e.g. SOLIDARITY trial drugs or antivirals) was noted. Most of the reports contain ADR terms describing the off-label use situation. A substantial number of these reported progressive disease or fatal outcome as an ADR; a similar number of reports merely stated, “no adverse reaction”.

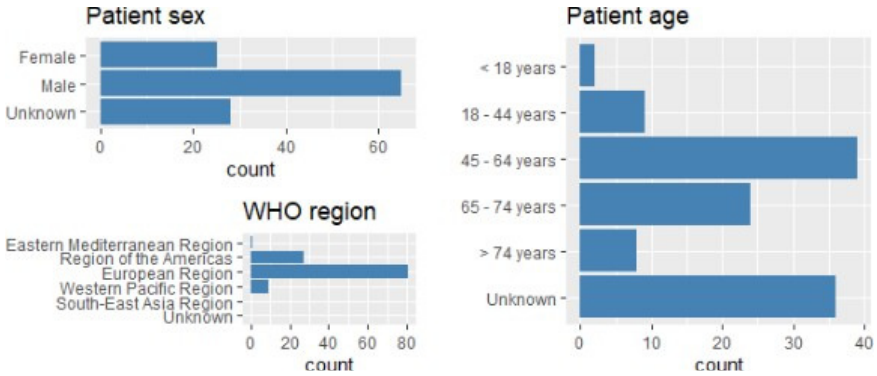

Figure 7. Demographics of VigiBase reports received cumulatively so far for Tocilizumab as suspected or interacting drug.

Adverse events

The pattern of reported ADRs was largely consistent with what is labelled for the drug.[3] The most commonly reported ADRs were as follows:

A substantial cluster of reports concerned hepatitis reactions, hepatocellular damage and a smaller number of reported hepatic laboratory abnormalities. Most reports of hepatitis did not contain narratives or data more closely describing the reactions, and most of them also contained several co-suspect drugs. Hepatitis is acknowledged in the labelling as a rare side effect for tocilizumab and transaminase and bilirubin increases as common ones.[3] COVID-19 may also present with transaminase increase and in patients with more severe disease with liver damage, while it is unknown if this is causally related to the COVID-19 infection or due to other factors.[6]

Another cluster of reports, (all lacking narratives) pertained to white blood cell disorders which are labelled with a frequency of common[3] for the drug and may also be present in the disease.

A group of anaphylactic reactions and cardiac arrhythmias, including cases of asystole occurring on the day of the infusion were reported; several of them fatal. Anaphylaxis is labelled for the drug while cardiac side effects are not but known as part of the disease. The cases may serve as reminders of the need for closely monitoring patients while receiving tocilizumab.

Among other reactions reported and described in the product label for the drug are gastrointestinal perforations and bleedings, thrombocytopenia and hypotension.[3] Pancreatitis reactions are not among labelled reactions.[3], however it was identified by the FDA as potential signal in July 2017 and last reviewed in January 2018.[7]

The risk of developing severe infections and reactivating latent infections is known for tocilizumab where active infection constitutes a contraindication[3] and strict warnings and precautions are given.[3, 4] Acknowledging that all the reports in this review likely concerned COVID-19-infected patients, there are many reports describing concomitant antibacterial treatment which is also to be expected. There were further cases reporting severe infections which may be related to the known risk factor of the tocilizumab treatment per se, such as sepsis, septic shock, staphylococcal bacteraemia and a case of a dural abscess.

Disclaimer

Data in the reports are not complete and only a subset of the reports in the 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 of reports was carried out and may require further follow-ups. Any signals detected from this monitoring will be communicated separately.

Errata from report dated 2020-04-19

In the third report, the count of new hydroxychloroquine reports was said to be 127 in table 1. This was incorrect, the actual count was 113, and the remaining 14 were already included from a previous report.

References

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5. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. The Journal of infection. 2020.
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Drug group	N_old	N_new	N_total
Azithromycin	95	254	349
Chloroquine	32	143	175
Hydroxychloroquine	210	360	570
Lopinavir;Ritonavir	156	87	243
Remdesivir	40	16	56
Tocilizumab	35	83	118
Other drugs	30	57	87
Unique reports	460	686	1146

Table 1. N_old display reports entered in VigiBase no later than the 19th of April. N_new between 20th of April and 3 of May. Other drugs are selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase.
Counts include suspected or interacting drugs. As one report may contain several drugs, rows are not mutually exclusive.

		Azithromycin		Chloroquine		Hydroxychloroquine		Lopinavir;Ritonavir		Remdesivir		Tocilizumab		Other		Unique reports	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Report characteristics																	
	Total N	349	100	175	100	570	100	243	100	56	100	118	100	87	100	1146	100
	Single Susp.	14	4	71	40.6	287	50.4	177	72.8	55	98.2	90	76.3	40	46	734	64
	Serious	186	53.3	65	37.1	381	66.8	127	52.3	27	48.2	84	71.2	38	43.7	661	57.7
	Fatal	18	5.2	2	1.1	31	5.4	15	6.2	9	16.1	38	32.2	16	18.4	102	8.9
Sex																	
	Female	149	42.7	100	57.1	204	35.8	73	30	10	17.9	25	21.2	36	41.4	408	35.6
	Male	188	53.9	68	38.9	351	61.6	167	68.7	44	78.6	65	55.1	45	51.7	677	59.1
	Unknown	12	3.4	7	4	15	2.6	3	1.2	2	3.6	28	23.7	6	6.9	61	5.3
Age																	
	Median (Q1-Q3)	55 (41-67)		53 (36-65)		59 (47-71)		64 (55-73)		55 (41-65)		62 (53-67)		58 (44-70)		60 (47-71)	
	< 18 years	5	1.4	4	2.3	5	0.9	2	0.8	2	3.6	2	1.7	1	1.1	14	1.2
	18 - 44 years	86	24.6	55	31.4	107	18.8	17	7	15	26.8	9	7.6	21	24.1	204	17.8
	45 - 64 years	132	37.8	61	34.9	213	37.4	95	39.1	18	32.1	39	33.1	32	36.8	414	36.1
	65 - 74 years	67	19.2	32	18.3	117	20.5	68	28	11	19.6	24	20.3	15	17.2	242	21.1
	> 74 years	35	10	10	5.7	99	17.4	46	18.9	2	3.6	8	6.8	14	16.1	171	14.9
	Unknown	24	6.9	13	7.4	29	5.1	15	6.2	8	14.3	36	30.5	4	4.6	101	8.8
WHO region																	
	African Region	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Eastern Mediterranean Region	124	35.5	105	60	37	6.5	1	0.4	0	0	1	0.8	0	0	141	12.3
	European Region	204	58.5	42	24	432	75.8	232	95.5	56	100	81	68.6	75	86.2	819	71.5
	Region of the Americas	13	3.7	3	1.7	79	13.9	1	0.4	0	0	27	22.9	3	3.4	113	9.9
	South-East Asia Region	2	0.6	3	1.7	13	2.3	0	0	0	0	0	0	0	0	16	1.4
	Western Pacific Region	6	1.7	22	12.6	9	1.6	8	3.3	0	0	9	7.6	9	10.3	56	4.9
	Unknown	0	0	0	0	0	0	1	0.4	0	0	0	0	0	0	1	0.1

Table 2. Other drugs are selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase. Single susp. = Drug was reported as single suspected or interacting drug, Q1-Q3 = First to third quartile. Counts are cumulative and include suspected and interacting drugs. As one report may contain several drugs, columns are not mutually exclusive.

Drug	N	%
Unique reports	87	100
Oseltamivir	57	65.5
Ritonavir	15	17.2
Darunavir	13	14.9
Baricitinib	9	10.3
Plasma	8	9.2
Cobicistat;Darunavir	7	8
Eculizumab	6	6.9
Canakinumab	4	4.6
Interferon beta	4	4.6
Interferon beta-1a	4	4.6
Anakinra	3	3.4
Siltuximab	3	3.4
Lopinavir	2	2.3
Almitrine	1	1.1
Icatibant	1	1.1
Octreotide	1	1.1
Umifenovir	1	1.1

Table 3. Drugs included in the Other drugs-category. Counts are cumulative and include drugs reported as suspected or interacting. As one report may contain several drugs, rows are not mutually exclusive.

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.