

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 fifth summary of global reporting of ADRs for drugs used to treat COVID-19 is mainly descriptive in nature. It includes reviews for the drugs in the WHO SOLIDARITY trial and other drugs used for a COVID-19 indication, and where the number of reports exceeds 100.

Reports have now been shared from five of the six WHO regions, with the largest number still originating in the WHO European Region. The reported ADRs largely continue to be those included in available product labelling or information; QT prolongation and hepatic events are the most commonly reported events. Of note are the concomitant use of multiple interacting medications and the occurrence of individual cases of serious events such as DRESS, completed suicide and sudden death which will remain under surveillance in future reviews.

Reports in VigiBase

The methodology of search has been refined for this fifth review. Reports were screened for drugs given on a Corona or COVID-19 indication, by relevant free-text terms and laboratory tests. Reports without a decisive COVID-19 indication were reviewed manually before inclusion. For this reviewing period, we have also noted that the new MedDRA-terms for COVID-19 are already being reported from National Centres. Reports were received at the National Centres between 1st November and 10th May 2020 and were reported to VigiBase no later than 10th May. Reports were included when they reported as suspected/interacting drugs in the SOLIDARITY trial or drugs considered clinically relevant based on medical-expertise and reported to VigiBase on a Corona or COVID-19 indication. See Table 3 in appendix.

Note that there is country-specific reporting delay after receipt of reports at National Centres, thus the reporting date to VigiBase should not be considered as proxy for reporting date to National Centres, or, the date of adverse events. See Figure 1 for a visualisation of the arrival dates at National Centres for this reviewing period.

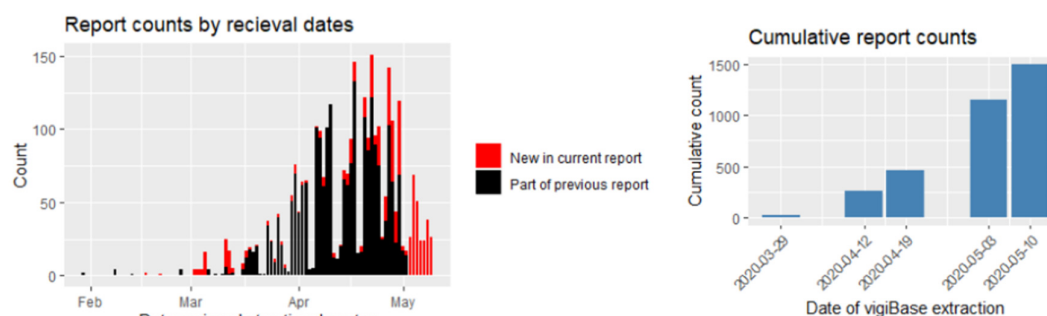


Figure 1. Number of reports by dates received at national center (left), and cumulative number of reports in VigiBase at the dates of extractions for reports. The rightmost bar (right panel) shows the total number of reports received so far.

When retrieving and reviewing relevant ADR reports for this analysis, reports without specific COVID-19 treatment-related ADRs have been observed. Examples are: 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 hope of reducing the risk of developing COVID-19 disease. Reports on use in asymptomatic individuals were also observed and are included in the review.

Traces of the pandemic's effect on health-care and drug-use patterns is visible in the ADR reporting.

Characteristics of the reports, regardless of medicinal products

Since the last analysis, 353 new case reports have been identified using the selected search strategy (Table 1). Cumulatively, there have been a total of 1491 reports from 5 WHO regions with the large majority from the European region (66.2 %). 55.9 % of the reports were classified as "serious" (Table 2) but not all reporting standards used include seriousness (e.g. INTDIS). Males accounted for 58.4 % 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 2. In line with males being more affected by COVID-19 infection globally, for all drugs except chloroquine, the reporting for all drugs was most prevalent for males. Patient ages were similar between drugs, although lopinavir;ritonavir had the highest median age.

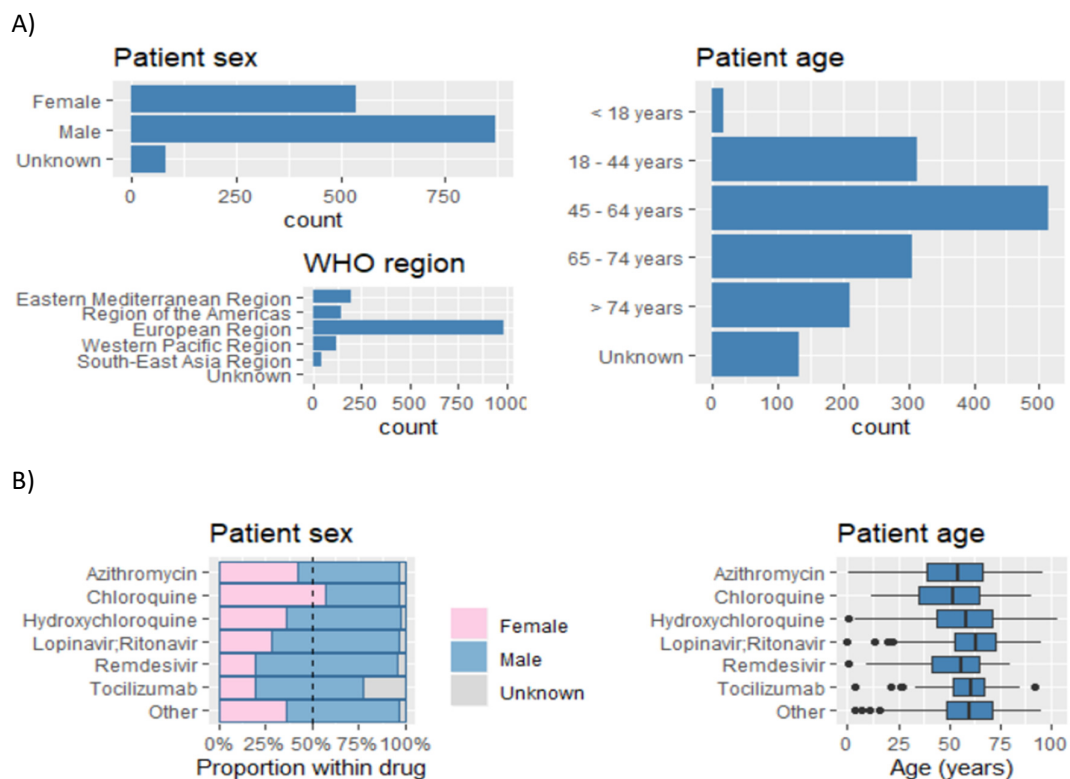


Figure 2. Overall demographics of case safety reports sent into VigiBase in treatment of COVID-19. A) All reports. B) Reports by drug. The B) graphs rely on counts of reports which include each drug as suspected or interacting. Reports including several drugs will be counted once for each reported drug. Patient age boxes show medians and interquartile ranges.

Characteristics of the reports for WHO Solidarity trial drugs

Hydroxychloroquine alone or in combination with azithromycin

There were 192 new reports for hydroxychloroquine during this review period, adding to a cumulative total of 757 reports with cumulative demography shown in Figure 3. The new reports included 112 men, 73 women and seven with unknown sex. The new reports were shared from the European region (89), Region of the Americas (24), Eastern Mediterranean region (36), South East Asia (26) and Western Pacific region (17). In the new reports there were 69 reports in the age group 18-44 years, 50 reports in the age group 45-64 years, 39 reports in the age group 65-74 years, 23 reports in the age group 75 years and above and nine reports of unknown age. For the new reports, hydroxychloroquine was a single suspected drug in 105 cases.

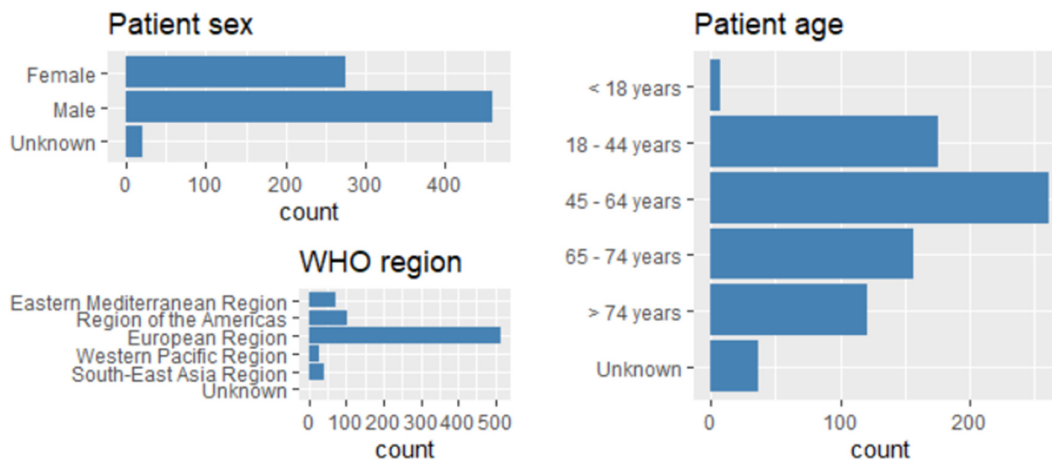


Figure 3. Demography of Vigibase reports received cumulatively so far on hydroxychloroquine as suspected or interacting drug.

Adverse events

Among the reported preferred terms with the highest increase in the number of reported cases to Vigibase during this period were Electrocardiogram QT-prolongation (for the fifth time in a row) followed by the terms diarrhoea, intentional product use issues which mainly included off-label use, hepatitis and palpitations.

Electrocardiogram QT-prolongation (31 cases during the review period, 209 cases cumulative). Cases submitted from seven countries spread over four regions. More than half of the cases (23) were reported as serious with four fatal outcomes. The reports included 21 male and 10 females, the majority (12) being between 65-74 years of age. Electrocardiogram QT-prolongation has been seen to be dose-related, however the ADR was reported with doses below the maximum recommended dose in 22 of the 31 cases, indicating that the ADR may occur even with normal doses.¹ In nine of the new cases, doses that exceeded recommended doses were given, with a dosage ranging between 600 mg to 2400 mg a day. Hydroxychloroquine was co-administered with azithromycin in 12 cases and given as a single drug in 19 cases. Lopinavir/Ritonavir had been co-administered in two cases.

Hepatitis (10 cases during the review period, 56 cases cumulative). The ADR is not labelled for hydroxychloroquine, but in all cases, there were co-reported drugs that have hepatitis labelled in their product information. On screening the literature, a case report was found that described a patient who developed hepatitis after receiving hydroxychloroquine but recovered after the drug was withdrawn.²

Palpitations is an ADR that had seven new reports. When evaluating the cases that have been submitted from four different countries and regions, we could see that some of the cases, where the ADR was reported, concerned health-care professionals who had taken hydroxychloroquine as a prophylaxis when treating COVID-19 patients. Palpitations may occur with overdoses of hydroxychloroquine but for these reported cases, only two of the cases reported high doses, three cases included doses within the range recommended in labelled indication, while the remaining cases did not include any dose information.

Sudden death (one case during the reporting period, six cases cumulatively). All six cases are reviewed here. Ages ranged from 39-82 years, with four males and two females. Cases originated from three countries. Five cases reported interacting concomitant medications including azithromycin, levofloxacin, lopinavir/ritonavir, ceftriaxone, metoclopramide, quetiapine, risperidone. Concomitantly reported ADRs were cardiac arrest in one case, long QT syndrome in another. Literature describes a risk of a synergistic effect between hydroxychloroquine and azithromycin, which can be toxic for patients.³

Psychiatric adverse events. A number of psychiatric events were noted during the review period, including behaviour disorder, factitious disorder, aggression and confusional state. Cumulatively, additional events have been reported, including nightmare, psychotic behaviour, sleep disorder, sopor, hallucination visual (two cases), agitation (three cases), hallucination (three cases) and completed suicide (three cases). In two of the three completed suicide cases, the term agitation was co-reported which has been seen for hydroxychloroquine used in the context of malaria as a result of its effect on the central-nervous-system.⁴

Chloroquine

During this review period 33 new reports, in which chloroquine was reported as suspecting or interacting drug, were reviewed. These concerned 15 male and 18 female patients; median age of patients described in the new reports was 42 years. 17 reports originated from the WHO Eastern Mediterranean Region, 10 from the WHO Western Pacific region. An overview of the cumulative reporting demography is shown in Figure 4.

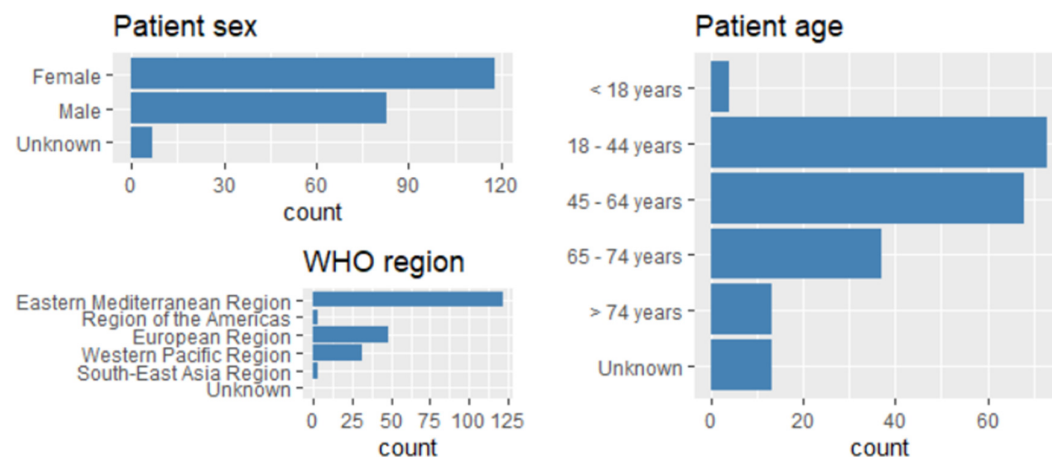


Figure 4. Demographics of Vigibase reports received cumulatively so far for chloroquine as suspected or interacting drug.

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 28 serious reports, two reports included at least one of the following Preferred Terms: Electrocardiogram QT prolonged (five reports), Vomiting (three reports), Nausea (two reports), Diarrhoea (two reports), Headache (two reports).

All of the reported adverse events above are included in the Summary of Products Characteristics of chloroquine.⁵

One serious report (outside of the counts in the paragraph above) describes the daily intake of 1000mg of chloroquine for a week in an adult male, leading to overdose characterised by seizures and orthostatic hypotension with outcome unknown.

Azithromycin

Reports including azithromycin are largely described in the sections of chloroquine, hydroxychloroquine or lopinavir;ritonavir.

We identified seven cases from three different countries where azithromycin was taken as the only drug, for the indication COVID-19 in six out of the seven cases, and in one case, for pneumonia. The reports contained non-serious reactions which mostly have been labelled for azithromycin.⁶

An overview of the cumulative reporting demography is shown in Figure 5.

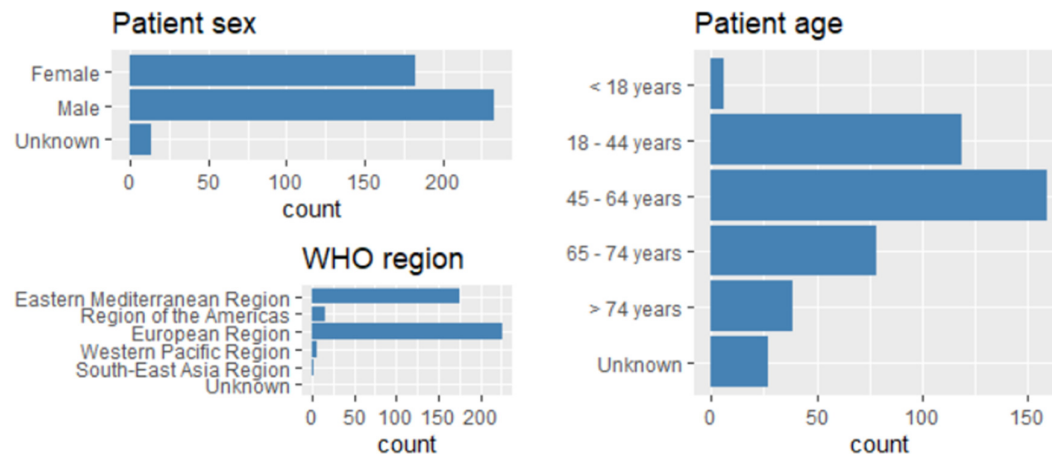


Figure 5. Demography of Vigibase reports received cumulatively so far on azithromycin as suspected or interacting drug.

Lopinavir;ritonavir

During this review period 69 new reports, in which lopinavir;ritonavir were reported as suspected or interacting drugs, were reviewed. These concerned 46 male and 16 female patients; median age of patients described in the new reports was 59 years (seven reports had no age reported). 33 reports originated from the WHO European region and 35 from the WHO Western Pacific region. An overview of the cumulative reporting demography is shown in Figure 6.

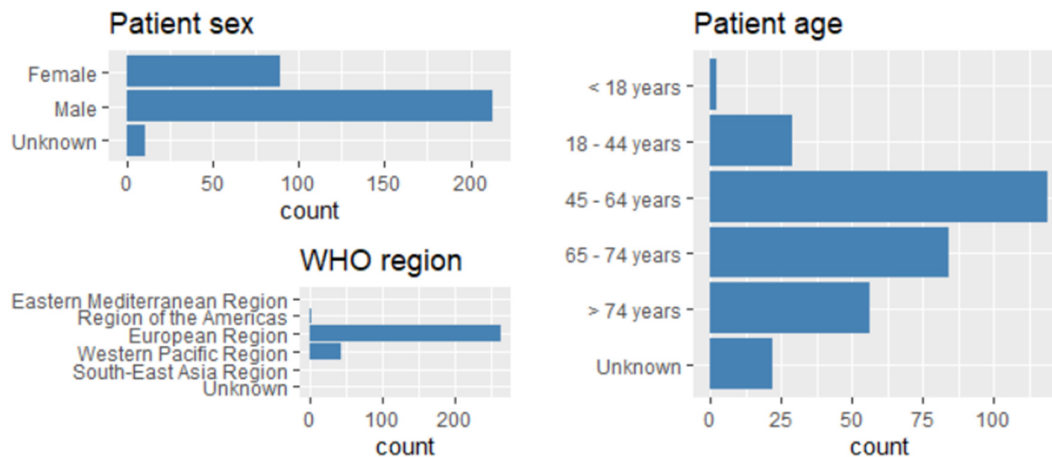


Figure 6. Demographics of VigiBase reports received cumulatively so far for lopinavir;ritonavir as suspected or interacting drug.

Adverse events

The most commonly reported ADRs continued to be those which are included on the product labelling for lopinavir;ritonavir.⁷

The most commonly reported ADRs during the review period were diarrhoea (14 reports), nausea (five reports) and vomiting (five reports).

The most commonly reported ADRs cumulatively are: diarrhoea (79 reports), hepatocellular injury (31 reports), nausea (30 reports), electrocardiogram QT prolonged (23 reports), and vomiting (16 reports)

Off-label use has been reported as an ADR in 11 reports during the review period and in 88 reports cumulatively.

Reports related to hepatic system continue to be received. In addition to hepatocellular injury as noted above, there were new reports for hypertransaminasemia (two new, 11 cumulative), hepatitis (two new, 14 cumulative), hyperbilirubinemia (two new, 15 cumulative), and hepatic enzyme increased (three new, eight cumulative).

Newly reported ADRs of interest include: tinnitus (one report), jaundice cholestatic (one report), type I hypersensitivity (one report), blood creatinine increased (one report), glomerular filtration rate abnormal (one report).

Reports on hypertriglyceridemia and pancreatitis were mentioned in the previous review. There were no new reports received in this period. Hyperglyceridaemia and pancreatitis are both included in the product labelling.

Reports on rhabdomyolysis were mentioned in the previous review. There were no new reports received in this period.

Remdesivir

There are currently a total of 67 reports of remdesivir in VigiBase of which 10 were received in the current review period. In eight of these 10, remdesivir was the single drug reported as suspected for the adverse events reported. The reports concerned six female and three male patients as well as one patient of unknown sex. All 10 reports shared during this period originated from the WHO European region. As remdesivir is not yet evaluated and approved through normal regulatory procedures, a short summary of every case is included in the report. An overview of the cumulative reporting demography is shown in Figure 7.

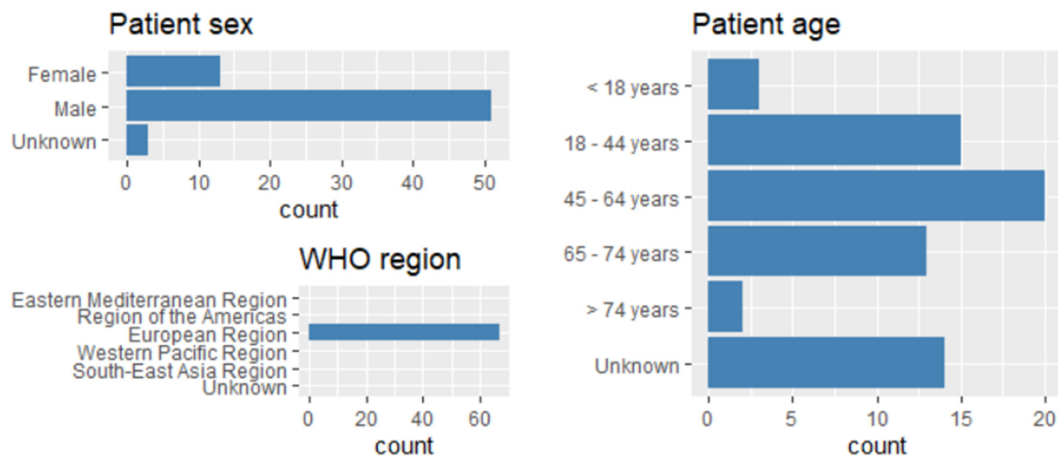


Figure 7. Demography of VigiBase reports received cumulatively so far on remdesivir as suspected or interacting drug.

Adverse events

In previous reports, the most commonly reported suspected reactions for remdesivir were hepatobiliary-related events (SOC Hepatobiliary disorders, SOC Investigations). In this period however, seven out of ten of the reports describe renal events (Renal and urinary disorders SOC, Investigations SOC). The preferred terms mentioned were, in four cases, acute kidney injury, one report of dysuria, one of glomerular filtration rate abnormal and one of glomerular filtration rate decreased. Three reports mentioned hepatobiliary-related events; one reported hyperbilirubinemia, one transaminases increased and one liver function test abnormal. The last report mentioned a cause of accidental occupational exposure to remdesivir. A short summary of each report is available in the section below.

Renal events

Seven out of ten of the reports for this period describe renal events (Renal and urinary disorders SOC, Investigations SOC), these are summarized below. It should be noted that the pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment; patients with eGFR greater than or equal to 30 mL/min have been reported to have received remdesivir for treatment of COVID-19 without dose adjustment.⁸ The eGFR at initiation of remdesivir was not recorded in the reports in VigiBase for the patients reporting renal adverse events.

The first case had remdesivir as the only suspected drug for the adverse events hyperbilirubinemia and acute kidney injury. The hyperbilirubinemia was reported with a time to onset of six days and a duration of 20 days. After removal of the drug the hyperbilirubinemia was reported as recovered. The acute kidney injury had a time to onset of five days and the patient was reported as not recovered.

The second case describes acute kidney injury with a time to onset of two days after the initiation of remdesivir. Potential confounding factors include concomitant medications, furosemide and ioprimide as well as sepsis/volume overload in this patient with type II diabetes.

The third case was treated with remdesivir for three days. The reported adverse events were pulmonary thrombosis after two days, acute kidney injury with a time to onset of four days and multiple organ dysfunction syndrome with an unknown time to onset. The drug was withdrawn and the outcome was death.

The fourth case reported multiple organ dysfunction syndrome with a time to onset of 16 days and acute kidney injury with a time to onset of 17 days. The outcome was reported as death. Cause of death was assessed as multi-organ failure.

The fifth case reported glomerular filtration rate decreased the same day as start of drug. The drug was withdrawn and outcome was recorded as 'death'.

The sixth case reported glomerular filtration rate abnormal with a time to onset of five days. The drug was withdrawn and the outcome was 'not recovered'.

The seventh case was a patient treated with remdesivir for three days. The adverse events reported were dysuria reported at the same day as start of drug intake, hyperkalemia with a time to onset of one day, abdominal discomfort and edema with a time to onset of two days. The hyperkalemia and abdominal discomfort were reported as recovered, the rest as not recovered upon removal of drug.

Other adverse events

There were three reports with non-renal adverse events reported:

The first case reported transaminases increased with a time to onset of 14 days and respiratory failure. The drug was reported to have been withdrawn and the outcome as death.

The second report describes an occupational exposure to the product, ocular hyperaemia, eye pruritus, rash pruritic and rash erythematous with a reaction duration of one day before the patient recovered.

The third case reported atrial fibrillation and liver function test abnormal. Atrial fibrillation was reported with a time to onset of two days after which the drug was withdrawn and the patient recovered from the event. The time to onset of liver function test abnormal was three days and the outcome and other information about the liver function test abnormal was reported as unknown.

Elevated transaminases, as seen above in the first of the non-renal cases reported for this period, have previously been reported⁸ and additional cases reported to Vigibase have also been described in earlier reports.⁹

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

A number of cases identified report the use of other drugs than the WHO-solidarity ones for the treatment of COVID-19. See Table 3. The number and diversity of the drugs used continue to increase.

As ADR data accumulate for other substances used for COVID-19, treatment and patterns of reported adverse events for them will be described in subsequent reports. A more detailed review of a drug is included in this report once a total of 100 reports is reached. Tocilizumab remains the only such drug and is reviewed below.

Tocilizumab

Tocilizumab is a monoclonal antibody against the interleukin-6 receptor. Approved indications are all non-infectious in nature and among them and most relevant for its use in COVID-19, is cytokine release syndrome (CRS).^{10,11} The drug is used in COVID-19 to alleviate the inflammatory cytokine storm, part of a severe inflammatory response to the viral infection.

During this review period there were 23 new reports in which tocilizumab was reported as suspected or interacting, adding up to a cumulative number of 141 reports. An overview of the cumulative reporting demography is shown in Figure 8. New reports concerned 16 males,

three females and four where gender was not reported; median age of the patients was 59 (with three reports lacking information on age). The new reports were shared from the European region (20), Region of the Americas (one) and the Western Pacific region (two).

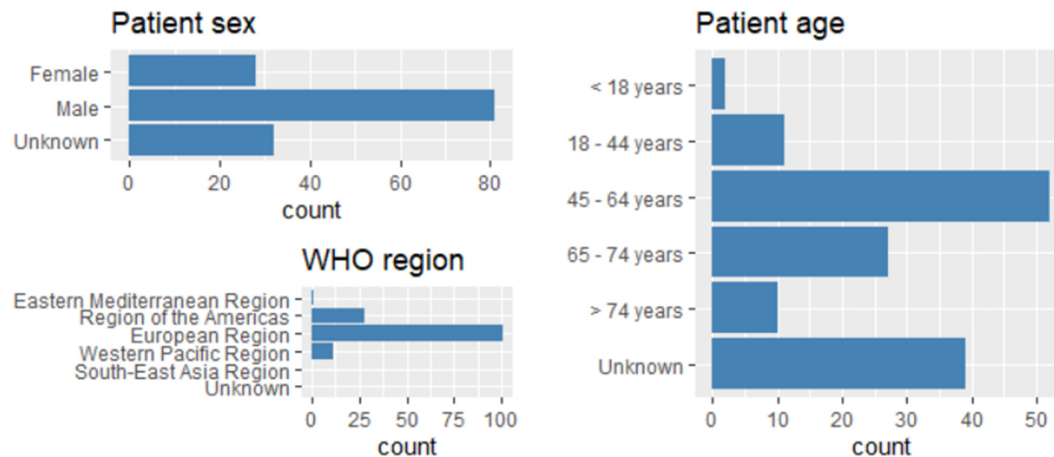


Figure 8. Demographics of VigiBase reports received cumulatively so far for tocilizumab as suspected or interacting drug.

Adverse events

Since the last review an increase in reports of coagulopathies and platelet disorders is noted. The most common reaction of the type is hypofibrinogenemia with four new reported cases, making up a total of nine. While hypofibrinogenemia is in the label as a common adverse event^{10,11} for tocilizumab, there is neither further characterisation of this risk nor detailed precautions or recommendations for dose adjustment should it occur. Hypofibrinogenemia might remain asymptomatic while inherently it increases the risk of bleeding.¹² The time to onset in the reports was between 3-8 days and in most cases, it was co-reported with one or more coagulation-related term representing either thromboembolic or haemorrhagic events.

Cumulatively, 15 cases of coagulation related reactions have been reported. Besides hypofibrinogenemia, reported reactions are thrombocytopenia, coagulopathy, hypocoagulable state, haemorrhage terms (e.g. cerebral, gastrointestinal), fibrin D dimer and interleukin level disturbances, thromboses and emboli. Seven of the cases had a fatal outcome; two of which were patients in their twenties, both with recent surgical major events in their medical history. Reports include those with tocilizumab as a sole reported agent (n=7) as well as reports with concomitant use of WHO Solidarity trial drugs and/or anticoagulants and antibiotics (n=8). A collected assessment of the cases is one of complicated coagulation system imbalance where the inherent ability of the drug to cause bleedings cannot be excluded as adding to the clinical picture as may have the COVID-19.

In the previous review (#4 (2020-05-12)), case series of reports for hepatic reactions, white blood cell disorders, anaphylactic reactions, cardiac arrhythmias, and severe infections (other than COVID-19) were discussed; an update follows: In this review, there were two additional reports of hepatitis, acknowledged in the labelling as a rare side effect for tocilizumab.¹⁰ In both cases the time to onset was two days and the patients recovered after withdrawal of tocilizumab and the other co-suspect drugs: levofloxacin and a combination of azithromycin, ceftriaxone and hydroxychloroquine respectively. COVID-19 may 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.¹³

There were two additional reports of neutropenia and leukopenia where tocilizumab was the sole reported (and suspect) drug with a time to onset of 23 and 10 days respectively; both reporting recovery after drug withdrawal. White blood cell disorders are labelled with a frequency of common¹⁰ for the drug and may also be present in the disease.

Following the anaphylactic reactions case series of the last review, there were now one case of hypersensitivity reaction with sparse information, one reporting urticaria with a time to onset of one day in a case with several other concomitant drugs and one case of DRESS, gastrointestinal bleeding and hypofibrinogenemia (also included above), with five co-suspect drugs and a time to onset (as regards tocilizumab) of 21 days. Urticaria and hypersensitivity are labelled for the drug, but not DRESS.

In addition to cases of infection and the discussion related to the risk of infections in relation to tocilizumab use in the last review, there are in this review three opportunistic infections reported in two patients: one of bronchopulmonary aspergillosis and a combination of candida infection and genital herpes.

Tocilizumab and most of the other drugs outside the Solidarity-trial drug arsenal mentioned above are mainly used to treat the secondary host response to the infection, a response that is often of inflammatory nature.

The pattern of reported ADRs lies largely within what is labelled for the drug.^{10,11}

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 deduplication was used. Any signals detected from this monitoring will be communicated separately.

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Drug group	N_old	N_new	N_total
Azithromycin	347	81	428
Chloroquine	175	33	208
Hydroxychloroquine	565	192	757
Lopinavir;ritonavir	243	69	312
Remdesivir	57	10	67
Tocilizumab	118	23	141
Other drugs	127	70	197
Unique reports	1138	353	1491

Table 1. N_old display reports described in previous reports, which included reports received to VigiBase no later than the 3rd of May. N_new includes reports received to VigiBase no later than the 10th of May. Other drugs are selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase, see Appendix. 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	428	100	208	100	757	100	312	100	67	100	141	100	197	100	1491	100
	Single Susp.	16	3.7	78	37.5	337	44.5	167	53.5	59	88.1	101	71.6	73	37.1	831	55.7
	Serious	214	50	76	36.5	460	60.8	178	57.1	36	53.7	104	73.8	117	59.4	834	55.9
	Fatal	23	5.4	3	1.4	48	6.3	20	6.4	13	19.4	49	34.8	28	14.2	140	9.4
Sex																	
	Female	182	42.5	118	56.7	276	36.5	89	28.5	13	19.4	28	19.9	76	38.6	537	36
	Male	233	54.4	83	39.9	460	60.8	213	68.3	51	76.1	81	57.4	110	55.8	871	58.4
	Unknown	13	3	7	3.4	21	2.8	10	3.2	3	4.5	32	22.7	11	5.6	83	5.6
Age																	
	Median (Q1-Q3)	54 (39-66)		52 (35-65)		58 (44-71)		63 (53-73)		56 (41-65)		61 (51-67)		58 (44-70)		59 (45-70)	
	< 18 years	6	1.4	4	1.9	7	0.9	2	0.6	3	4.5	2	1.4	2	1	17	1.1
	18 - 44 years	119	27.8	73	35.1	175	23.1	29	9.3	15	22.4	11	7.8	45	22.8	312	20.9
	45 - 64 years	159	37.1	68	32.7	261	34.5	119	38.1	20	29.9	52	36.9	75	38.1	514	34.5
	65 - 74 years	78	18.2	37	17.8	156	20.6	84	26.9	13	19.4	27	19.1	36	18.3	306	20.5
	> 74 years	39	9.1	13	6.2	121	16	56	17.9	2	3	10	7.1	25	12.7	210	14.1
	Unknown	27	6.3	13	6.2	37	4.9	22	7.1	14	20.9	39	27.7	14	7.1	132	8.9
WHO region																	
	African Region	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Eastern Mediterranean Region	175	40.9	122	58.7	73	9.6	1	0.3	0	0	1	0.7	5	2.5	197	13.2
	European Region	227	53	48	23.1	516	68.2	265	84.9	67	100	101	71.6	162	82.2	987	66.2
	Region of the Americas	16	3.7	3	1.4	103	13.6	2	0.6	0	0	28	19.9	12	6.1	146	9.8
	South-East Asia Region	3	0.7	3	1.4	39	5.2	0	0	0	0	0	0	0	0	43	2.9
	Western Pacific Region	7	1.6	32	15.4	26	3.4	43	13.8	0	0	11	7.8	18	9.1	117	7.8
	Unknown	0	0	0	0	0	0	1	0.3	0	0	0	0	0	0	1	0.1

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



Drug	N	%
Unique reports	197	100
Enoxaparin	41	20.8
Oseltamivir	38	19.3
Favipiravir	17	8.6
Ritonavir	15	7.6
Heparin	13	6.6
Darunavir	12	6.1
Baricitinib	9	4.6
Plasma	9	4.6
Eculizumab	6	3
Ribavirin	6	3
Canakinumab	5	2.5
Cobicistat;Darunavir	5	2.5
Metamizole	5	2.5
Ruxolitinib	4	2
Siltuximab	4	2
Ascorbic acid	3	1.5
Interferon beta-1b	3	1.5
Lopinavir	3	1.5
Rituximab	3	1.5
Sarilumab	3	1.5
Umifenovir	3	1.5
Zinc	3	1.5
Anakinra	2	1
Interferon beta-1a	2	1
Ivermectin	2	1
Ademetionine	1	0.5
Almitrine	1	0.5
Bromhexine	1	0.5
Ciclosporin	1	0.5
Colchicine	1	0.5
Epoprostenol	1	0.5
Icatibant	1	0.5
Immunoglobulin human normal	1	0.5
Interferon beta	1	0.5
Octreotide	1	0.5
Tofacitinib	1	0.5

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.

	Azithromycin	Chloroquine	Hydroxychloroquine	Lopinavir;Ritonavir	Remdesivir	Tocilizumab
Total (S/I/C)	517	218	855	342	67	161
Single suspected	16	78	337	167	59	101
Azithromycin		134	344	50	7	31
Chloroquine	134		4	18	1	5
Hydroxychloroquine	344	4		120	21	62
Lopinavir;Ritonavir	50	18	120		10	18
Remdesivir	7	1	21	10		4
Tocilizumab	31	5	62	18	4	
Anakinra			1			
Ascorbic acid	10	2	12	1	1	
Baricitinib	2		4			
Canakinumab			1			
Ciclosporin			3	1		
Cobicistat;Darunavir	2		5			1
Colechicine			2			1
Darunavir	3		9		1	1
Eculizumab			1			
Enoxaparin	83	14	120	29	15	15
Favipiravir	13		19	2		4
Heparin	6		11	13	9	4
Immunoglobulin human normal	1		1			1
Interferon beta			1	4		1
Interferon beta-1a				3		
Interferon beta-1b	1	1	5	5		
Ivermectin			1			1
Lopinavir	2		6			
Metamizole	5		11	2	1	4
Oseltamivir	36	1	54	10	2	3
Ribavirin			1	7	1	
Ritonavir	5		16		1	1
Rituximab				1		
Ruxolitinib			1			
Sarilumab	2		2			
Umifenovir				5		
Zinc	11	4	6			
Other	225	59	386	179	44	52

Table 4. Co-medication frequencies. First row gives total number of report including a drug irrespective of drug role (suspected/ interacting/concomitant). Second row gives number of reports on which the drug was the single suspected or interacting drug. Remaining rows give frequencies of co-reporting of a drug pair, irrespective of drug role.

CAVEAT DOCUMENT

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.