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)

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The UMC is engaged in sharing relevant aggregated data regarding ADR reporting with use of drugs for the treatment of covid-19 disease, with an initial focus limited to drugs included in the WHO SOLIDARITY trial. Future reviews will include additional therapeutic agents that are currently being investigated in clinical trials reported in the WHO International Clinical Trials Registry Platform. At present these reviews are only descriptive in nature. No signal detection or causality assessment has been carried out with these reports at the current time but is the aim of further analyses.

Summary

There was a large increase in the number of reports of suspected adverse drug reactions (ADRs) with the use of drugs used in the treatment of covid-19. Most reports were identified by searching for “coronavirus infection” as indication with the drugs currently being investigated in the Solidarity trial. Reports are from Europe, the Americas and the Western Pacific regions. The reported adverse events are largely in line with those listed in product labels or other available drug information.

Reports in VigiBase

The methodology of search has been refined for this review, and reports extracted were those with an indication field mapped to the PT MedDRA-term “coronavirus infection” in the database. A pilot search of reports with free-text terms (coronavirus, Wuhan coronavirus, COVID) has been carried out for a subset of drugs (hydroxychloroquine, azithromycin) but is not included in this update. Reports were received at the National Centres between 1 January and 12 April 2020, and were reported to VigiBase no later than 12 April 2020.

Characteristics of the reports, regardless of medicinal products

A total of 255 case reports were identified by the selected search strategy. Reports came from 15 countries from 3 regions: Europe (246 cases), the Americas (seven cases) and the Western Pacific (two cases). 58% (149) of the reports were classified as “serious”.

The age of the patients in the reports ranged from 5 days to 95 years. Males accounted for 66% (169) of the reports and females 32% (80).

Most of the reports included at least one of the SOLIDARITY drugs and are further reviewed below. The search also identified additional reports describing other drugs known to be used in the treatment of COVID-19 disease, such as tocilizumab (10 reports), chloroquine (11 reports), oseltamivir (four reports).

Characteristics of the reports for drugs included in the SOLIDARITY trial

*Hydroxychloroquine alone or with antibiotics other than azithromycin*

There were 49 reports in this subgroup; 5 were captured via free-text screening only. Thirty were in male patients and 14 in females. Median age was 68.5 years, with a range of 30 – 88. Thirty were serious, with three fatalities.

**Adverse events**

Twenty-four reports included cardiac adverse events, represented by the following MedDRA Preferred Terms: Electrocardiogram QT prolonged, atrioventricular block first degree, atrioventricular block second degree, cardiac arrest, sinus tachycardia, atrial fibrillation, Ventricular tachycardia. The time to onset for these events was reported in all reports and ranged between 0-4 days.

Seven reports included hepatic adverse events, represented by the following MedDRA Preferred Terms: hepatic function abnormal, hyperbilirubinaemia, hepatitis, transaminases increased. The time to onset for these events was included in all reports and ranged between 1 and 6 days.

Other reports included MedDRA Preferred Terms such as: abdominal pain upper, abdominal pain, diarrhoea, rash, rash maculopapular, rash vesicular, vascular device infection and deep vein thrombosis. This list is not extensive.

**Co-reported drugs**

Two reports included lopinavir;ritonavir as co-suspected, 5 as concomitant. Other co-suspected or concomitant antibiotics included: cefotaxime, ceftriaxone, amoxicillin;clavulanic acid, clarithromycin, spiramycin and levofloxacin; among co-reported antivirals: cobicistat;darunavir, oseltamivir, ritonavir, darunavir; another concomitant potentially for COVID-19 was tocilizumab, but it was only available in 1 report.

*Hydroxychloroquine in combination with azithromycin*

There were 51 reports in this subgroup; 14 were captured via free-text screening only. Thirty-seven were in males and 12 in females. Median age was 63 years, with a range of 28 – 84 years. Forty-eight were serious, with four fatalities.

**Adverse events**

Twenty reports included cardiac adverse events, represented by the following MedDRA Preferred Terms: Electrocardiogram QT prolonged, long QT syndrome, Electrocardiogram PR prolongation, Electrogram T wave inversion, atrioventricular block first degree, Bundle branch block left,
Bradycardia, cardiac arrest, Sinus bradycardia, sinus tachycardia, atrial fibrillation, Ventricular tachycardia, ventricular arrhythmia, cardiogenic shock. One of these reports included a suspected interaction between azithromycin and hydroxychloroquine, with azithromycin introduced two days after initiation of hydroxychloroquine. Another, with lopinavir;ritonavir. The time to onset for these events ranged between 1 and 8 days.

Twenty-three reports included hepatic adverse events, represented by the following MedDRA Preferred Terms: hepatic enzymes increased, liver injury, hepatitis, hepatitis acute, drug-induced hepatitis, cholestasis. 14 out of the 23 included ceftriaxone either as suspected or concomitant drug. In seven, azithromycin was introduced after hydroxychloroquine. The time to onset for these events was included in all reports and ranged between 1 and 14 days.

There were three reports of sudden death.

Five reports included terms such as rash, neutropenia, agranulocytosis, headache, ocular discomfort, anxiety, psychomotor hyperactivity, nightmare.

Co-reported drugs

Four reports included lopinavir;ritonavir as co-suspected. Other co-reported antibiotics included: ceftriaxone, amoxicillin;clavulanic acid; among co-reported antivirals: oseltamivir, ritonavir, darunavir; another concomitant drug, potentially for COVID-19 was tocilizumab, available in four reports.

Azithromycin, alone, or with other antibiotics

There were six reports in this subgroup. Two were in males, four in females. Median age was 57 years, with a range of 44 – 80. One was serious.

These reports include various MedDRA Preferred Terms, such as tongue dry, swollen tongue, tongue discolouration, rash, rash (reported as: “pruriginous generalised exanthema”), haematuria, nausea. Electrocardiogram QT prolonged appeared in two reports.

Two reports included lopinavir;ritonavir as co-suspected. Other co-suspected or concomitant antibiotics included: ceftriaxone, amoxicillin;clavulanic acid; another concomitant drug, potentially for COVID-19 was tocilizumab, but it was only available in one report.

Lopinavir;ritonavir

The use of lopinavir;ritonavir was reported in 100 cases. 66 in males, 33 in females. Ages ranged from 5 days to 95 years. 47 were reports were classified as “serious”.

Adverse events

The most commonly reported ADRs were diarrhoea, off-label use, and nausea. Most cases of diarrhoea and nausea were non-serious. Both are known “very common” ADRs for lopinavir/ritonavir.

Eighteen cases reported ADR terms indicative of liver injury (hepatocellular injury, increased bilirubin, cholestasis, increased AST, hepatitis, hypertransanemia, jaundice, hepatic enzyme
increased). Co-reported as suspecting or interacting were pantoprazole in all ADRs are considered to be known for lopinavir/ritonavir.

Ten cases reported ADR terms indicative of renal injury (oliguria, acute kidney injury). There were six reports of oliguria, all from France. There were only three reports in VigiBase previously. There were four reports with ADR terms acute kidney injury. There were 182 cases in Vigibase previously.

Five cases reported ADR terms suggestive of cardiac effects (electrocardiogram QT prolonged, bradycardia, sinus bradycardia, arrhythmia supraventricular, ventricular tachycardia). In two of the cases, hydroxychloroquine was also suspected.

Two cases of sudden death were reported from a single country, in subjects aged 95 years and 75 years; both reported levofloxacin as a co-suspected or interacting drug.

Co-reported drugs

Lopinavir/ritonavir was concomitantly administered with a number of other drugs, of specific note are those other drugs used for COVID-19 and drugs known to have interactions with lopinavir/ritonavir. 36 cases reported concomitant use of drugs with a putative efficacy against COVID 19: hydroxychloroquine (26 cases), azithromycin (9 cases), remdesivir (1 case).

Three cases were identified with concomitant use of drugs known to have interactions with lopinavir/ritonavir including midazolam, nicardipine, and simvastatin.

Remdesivir

There were 34 reports with remdesivir. 85% of these reports were in male patients, 12% in females, sex was not indicated in 3% of the reports. There was one report in the age group 12-18 years, six reports for the age group 18-44 years, 13 reports for 45-64 years, 10 reports for 65-74 years and two reports in the age group 75 years and older. Six cases were fatal.

Adverse events

Sixteen reports included hepatic adverse events, these were: transaminases increased (6), hepatic enzymes increased (5), alanine aminotransferase increased (3), alanine aminotransferase (1), hepatic function abnormal (1).

The other reported adverse events were: acute kidney injury (4), diarrhoea (3), hypotension (3), septic shock (3), acute respiratory distress syndrome (2), pyrexia (2), anaemia (2), rash (2), rash maculopapular (2), amylase increased, blood creatine phosphokinase increased, blood creatinine increased, C-reactive protein increased, condition aggravated, erythema, hallucination, Herpes simplex, hypersensitivity, hypoxia, insomnia, medication error, overdose, phlebitis, platelet count decreased, pneumonia, pneumothorax, psychomotor hyperactivity, pulmonary fibrosis, rash pustular, respiratory failure, thrombocytopenia, off-label use, Staphylococcal sepsis (all 1 each).

Details of fatal cases (age, sex and ADRs reported):
1. Male 66 years: Acute kidney injury, alanine aminotransferase increased and septic shock
2. Male 59 years: Pneumonia and Staphylococcal sepsis
3. Male 73 years: Blood creatinine increased, pulmonary fibrosis and acute respiratory distress syndrome
4. Male 65 years: Acute kidney injury, hypoxia, respiratory failure, renal failure
5. Male 80 years: Anaemia, thrombocytopenia, septic shock
6. Male 65 years: Systolic dysfunction

Co-reported drugs

In 21 cases it was the only reported drug and in 31 cases it was the only drug suspected for the reported adverse drug reactions

In the three reports that had co-suspected drugs for the adverse drug reactions these were: rash maculo-papular, erythema and hypersensitivity (piperacillin; tazobactam), elevated hepatic enzymes (lopinavir; ritonavir and piperacillin; razobactam), heparin induced thrombocytopenia and alanine aminotransferase reported as 166 U/L and rash (meropenem).

Neither summary of products characteristics nor product label are available for remdesivir. The EMA’s summary on compassionate use for remdesivir indicates that transient elevation of hepatic enzymes were recorded in healthy volunteers after repeated dosing. The same summary reports: “In rats microscopic changes in the kidney were seen in males administered ≥ 3 mg/kg/day and in females administered 10 mg/kg/day, and were consistent with a regenerative process secondary to a sustained, low-level injury to the cortical tubules”.

Disclaimer

Data in the reports are not complete and none of the reports in this analysis contained narratives. With the 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 has not been carried out automatically and may require further follow-ups. Any signals detected in the future will be communicated separately.

References