Analysis of Favipiravir Adverse Drug Reactions during COVID-19 Pandemic: A Retrospective Study Based on Iraqi Pharmacovigilance Center Database

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Abstract:

The "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" was the reason behind the recent pandemic "COVID-19" that started from Wuhan, china, and rapidly spread to many regions of the world. Research in Drug repurposing processes to treat this novel coronavirus involved many medications, one of the most discussed is Favipiravir. The objective of the current work was aimed towards Examining the cause, severity, preventability, predictability, and outcome of favipiravir-associated adverse events that had been reported in Iraq. In terms of adverse drug responses, "Gastrointestinal disorders" accounted for the majority (57.4%), followed by "Cardiac disorders" (35.2%), and "Investigations" (abnormal lab test results) (13%). The causality of these reactions Is majorly "Possible" (62%). Severity level 1 (40.9%) and 2 (41.8%). Ninety-nine percent of the ADRs are expected. The majority of the ADRs are non-Preventable (76.3%). The main outcome is Recovered / Resolved (44.5%). About (50%) of the ADRs were serious.

Keywords: COVID-19, SARS-COV-2, Favipiravir, coronavirus, pharmacovigilance, Iraq, Adverse events

تحليل التفاعلات الدوائية الضارة لعقار فافيبيرافير أثناء جائحة كوفيد-١٩. دراسة بأثر رجعي بناءً على قاعدة بيانات مركز اليقظة الدوائي العراقي ٢٠٢٠

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الخلاصة:

المتلازمة التنفسية الحادة لفيروس كورونا ٢ (SARS-CoV-2) هو الفيروس التاجي الفريد الذي تسبب في اندلاع مرض فيروس كورونا مؤخرًا ٢٠١٩ (كوفيد-١٩)، والذي بدأ في ووهان، الصين، في نهاية عام ٢٠١٩ وانتشر بسرعة في جميع أنحاء العالم. فافيبيرافير هو أحد الأدوية المعاد استخدامها لعلاج كوفيد-١٩. الهدف من الدراسة الحالية هو متابعة التفاعلات الدوائية الضارة لعقار فافيبيرافير المبلغ عنها في العراق وتقييم السببية وشدة التفاعل والخطورة وإمكانية الوقاية والتوقع ونتائج هذه التفاعلات الضائرة.

ارتبطت معظم التفاعلات الدوائية الضائرة بـ "اضطرابات الجهاز الهضمي" (٥٧,٤٪) تليها "اضطرابات القلب" (٣٥,٢٪) والفحوصات (اختلال الفحوصات المخبرية)١٣) ٪. (إن سببية هذه التفاعلات اغلبيتها "محتمل" ٦٢) ٪. (تقييم مستوى الخطورة كانت اغلبها في المستوى ١ (٤٠,٩٪) والمستوى ٢ (٤١,٨٪). تسعة وتسعون بالمائة من التفاعلات الدوائية الضائرة متوقعة. غالبية التفاعلات الدوائية الضارة لا يمكن الوقاية منها (٦,٣٧٪). النتيجة الاكثر شيوعا هي تعافي / تم حلها (٤٤,٥٪). حوالي (٥٠٪) من التفاعلات الدوائية الضارة كانت خطيرة.

كلمات مفتاحية: كوفيد-١٩، فافيبيرافير، كورونا فايروس، اليقظة الدوائية، العراق، التفاعلات الدوائية الضارة

Introduction:

NCP, or novel coronavirus pneumonia, first surfaced in Wuhan near the end of the year 2019 and quickly expanded. The cause of this infection was attributed to the novel coronavirus disease as confirmed by the World Health Organisation and it has been named COVID-19 [1].

Typically, the first signs are merely a moderate fever, cough, and sporadic dyspnea. A proportion of people with COVID-19 sickness might present with severe manifestations, such as shortness of breath and acute respiratory distress syndrome (ARDS), 5-8 days into their illness [2].

There isn't a specific antiviral medication available for COVID-19 right now. Therefore, it is crucial for the COVID-19 pandemic response to identify pharmacological therapy alternatives as soon as practical. Based on the fact which states that the genomic sequences of SARS-CoV-2 and SARS-CoV are 75–80 percent similar, the current treatment for SARS and MERS, Favipiravir, may be useful in the development of COVID-19 therapies [3, 4]. Favipiravir, also known as T-705, was initially developed in 2002 as an inhibitor to influenza virus replication process. [4] and it represents an example of an RNA-dependent RNA polymerase (RdRp) inhibitor. The mechanism of action of this drug is either acting as a nucleotide analogue specified to inhibit the RNA-dependent RNA polymerase of the virus It induces lethal mutagenesis once incorporation into viral RNA After being transformed by host enzymes to T-705-ribofuranosyl 5′-triphosphate, without harming human cells [5, 6].

Favipiravir may therefore have potential antiviral effects on SARS-CoV-2, which is an RNA virus. It has been shown that Favipiravir efficiently prevents SARSCoV-2 infection in Vero E6 cells (ATCC-1586) when used as a prodrug. Vero cells are derived from the kidney of an African green monkey, and are one of the more commonly used mammalian continuous cell lines in microbiology, and molecular and cell biology research [7].

An Adverse Drug Reaction (ADR) can be defined as a significantly detrimental or unpleasant response that occurs as a result of an intervention associated with the administration of a pharmaceutical product. Adverse reactions typically indicate a potential risk associated with subsequent administration and require measures such as avoidance, targeted therapy, adjustment of dosage regimens, or discontinuation of treatment with the product [8]. The following adverse reactions have been mentioned in the Summary of Product Characteristic (SMPC) and leaflet: “AST (GOT) increased, ALT (GPT) increased, γ-GTP increased, diarrhea, neutrophil count decreased, white blood cell count decreased, blood uric acid increased, blood triglycerides increased, rash, nausea, vomiting, abdominal pain, glucose urine present, eczema, pruritus, blood ALP increased, blood bilirubin increased, abdominal discomfort, duodenal ulcer, haematochezia, gastritis, white blood cell count increased, reticulocyte count decreased, monocyte increased, blood potassium decreased, asthma, oropharyngeal pain, rhinitis, nasopharyngitis, blood CK (CPK) increased, blood urine present, tonsil polyp, pigmentation, dysgeusia, bruise, vision

blurred, eye pain, vertigo and supraventricular extrasystoles".

The primary aims of this study were to provide a comprehensive description of the distribution of adverse drug reactions (ADRs) associated with favipiravir, as reported to the Iraqi pharmacovigilance centre. Additionally, the study attempted to investigate the underlying causes, severity, seriousness, preventability, projected result, and expectedness of these ADRs.

Subjects and Method:

This retrospective analysis utilised Individual Case Safety Reports (ICSR) obtained from the Iraqi Pharmacovigilance Centre Ministry of Health. The data was acquired via the assistance of VigiFlow - Iraq. VigiFlow is a monitoring tool provided by the Uppsala Monitoring Centre (UMC), an entity linked with the World Health Organisation (WHO), which is responsible for global surveillance of adverse drug reactions.

The demographic distribution of the study, the classification of adverse drug reactions (ADR), cause, severity, expectability, preventability, and seriousness were all evaluated. The study included 135 adverse drug reactions and 108 ICSR.

By employing the System Organ Classification (SOC), which categorizes adverse responses based on the affected system or organ, and utilizing the Preferred Term (PT) as the primary terminology for describing drug-related adverse reactions, in accordance with the medical dictionary for drug regulatory affairs (MedDRA) [9] The drug reactions were classified. The ADRs in PT were categorized into tables depending on their SOC distribution in order to present the number and percentage of reported ADRs.

"ADRs that met the WHO-UMC criteria for causality assessment were divided into certain, probable, potential, unlikely, unclassified, and unclassifiable categories. The WHO-UMC standards are displayed in [10]. The modified Hartwig and Seigel criteria are used to evaluate the severity of ADRs, which are divided into seven degrees of severity (From Level 1 to Level 7). [11]

The Summary of Product Characteristics (SmPC) for every medication approved throughout the marketing authorisation process provided the foundation for the expectedness analysis. Each stated ADR was checked to determine if it was in the SmPC; if it was, it was regarded as an anticipated ADR; if it wasn't, it was seen as an unexpected ADR [12].

According to the updated Schumock and Thornton criteria, which were based on the original Schumock and Thornton article published in 1992, the ADRs were either preventable or not based on the Schumock and Thornton online calculator. Seven different questions were to be answered; if any answer was yes, the ADR is preventable, if all the answers were no, the ADR is not preventable. When evaluating a specific instance, if we encounter any questions with ambiguous answers, this will be logged as a potentially avoidable ADR [13].

According to the International Council for Harmonization's E2D criteria, serious cases include those that are life-threatening, result in death, need or extend hospitalization, and create permanent or major disability, congenital anomalies, or other clinically significant conditions. Consequently, a serious case must meet at least one of the above criteria. The seriousness relies on the judgment of the initial reporting person that

The World Health Organisation (WHO) classified the recorded findings of each Individual Case Safety Report (ICSR) into distinct categories. These categories include "fatal," "not recovered/not resolved," "recovered/resolved," "recovered with sequelae," "recovering/resolving," and "unknown." This classification was applied when the relevant portion of the report did not contain the required information.

Result:

Regarding the usage of Favipiravir over 2020 in the COVID-19 pandemic, the "Iraqi

Pharmacovigilance Center" has evaluated and documented 108 instances with 135 adverse medication reactions, of which 27 individuals took solely Favipiravir. While Favipiravir was taken concurrently by the other 81 individuals. All instances are qualitatively examined, including 62 reports from men and 46 reports from women. The affected patients' ages range from 18 to 75, as indicated in Table 1. Regarding seriousness, 60 reports were considered serious (55.6%), 48 reports were deemed not serious (44.4%), and 1 report of a fatal case in 2020 was considered fatal (0.9%).

Table 1 patients age groups

Patient age	Count	Percentage
18 - 44 years	35	32.4
45 - 64 years	55	50.9
65 - 74 years	17	15.7
≥ 75 years	1	0.9

Regarding reporter qualification, 92 reported by pharmacist (85.2%) and 16 reported by other health professionals (14.8%)

The ADRs reported in the ICSRs is classified according to the system-organ classification (SOC) and mentioned precisely as a Preferred term (PT) as shown in (TABLE 2)

Table 2 Adverse drug reaction reported in the ICSRs

Reaction (MedDRA)	Count	Percentage
SOC: “Blood and lymphatic system disorders”	1	0.9
PT: Anemia	1	100.0
SOC: Cardiac disorders	38	35.2
PT: Tachycardia	37	97.4
PT: Bradycardia	1	2.6
SOC: Gastrointestinal disorders	62	57.4
PT: Constipation	16	25.8
PT: Diarrhoea	11	17.7
PT: Abdominal pain upper	10	16.1
PT: Nausea	10	16.1
PT: Vomiting	9	14.5
PT: Abdominal pain	5	8.1
PT: Abdominal discomfort	3	4.8
PT: Dyspepsia	1	1.6
PT: Gastroesophageal reflux disease	1	1.6
PT: Gastrointestinal haemorrhage	1	1.6
SOC: General disorders and administration site conditions	2	1.9
PT: Chills	1	50.0

Reaction (MedDRA)	Count	Percentage
PT: Pyrexia	1	50.0
SOC: Investigations (lab tests abnormalities)	14	13.0
PT: Hepatic enzyme increased	11	78.6
PT: “Alanine aminotransferase increased”	3	21.4
PT: “Aspartate aminotransferase increased”	3	21.4
PT: “Blood alkaline phosphatase increased”	1	7.1
SOC: Musculoskeletal and connective tissue disorders	1	0.9
PT: Pain in extremity	1	100.0
SOC: Nervous system disorders	4	3.7
PT: Loss of consciousness	2	50.0
PT: Coma	1	25.0
PT: Headache	1	25.0
SOC: Respiratory, thoracic and mediastinal disorders	1	0.9
PT: Cough	1	100.0
SOC: Surgical and medical procedures	1	0.9
PT: Prophylaxis of nausea and vomiting	1	100.0
SOC: Vascular disorders	1	0.9
LLT: Hypertension	1	100.0

Table 3 ADRs in the 27 patient that only used Favipiravir

ADRs	Count	percent
Abdominal pain	4	14.81%
Abdominal pain upper	6	22.22%
Anaemia	1	3.70%
Constipation	1	3.70%
Diarrhoea	3	11.11%
Dyspepsia	1	3.70%
Gastrointestinal haemorrhage	1	3.70%
Hepatic enzyme increased	9	33.33%
Tachycardia	1	3.70%
Total	27 patients	

Table 4 Other suspected/interaction concomitant drugs used in 81 patients alongside Favipiravir

Drug	Suspected/interacting	Concomitant	Total	Percentage
Enoxaparin	5	49	54	50.0
Azithromycin	45	5	50	46.3
Paracetamol	2	42	44	40.7
Cholecalciferol	0	27	27	25.0
Ascorbic acid	0	25	25	23.1
Zinc	0	22	22	20.4
Dexamethasone	3	11	14	13.0
Bromhexine	0	11	11	10.2
Ceftriaxone	2	9	11	10.2
Meropenem	2	7	9	8.3
Levofloxacin	1	8	9	8.3
Acetylcysteine	0	2	2	1.9
Ranitidine	0	2	2	1.9
Ceftazidime	0	2	2	1.9
AI: Tocilizumab	0	2	2	1.9
AI: Remdesivir	2	0	2	1.9

Table 5 Causality, severity, expectedness, preventability, outcome and seriousness assessment

Causality	Number of ADRs (%)
Certain	0 (0)
Probable/ Likely	1 (0.9)
Possible	67 (62)
Unlikely	40 (37)
Conditional/ Unclassified	0 (0)
Unassessable/ Unclassifiable	0 (0)
Level of severity	
Level-1	45 (40.9)
Level-2	46 (41.8)
Level-3	1 (0.9)
Level-4	17 (15.4)
Level-5	0 (0)
Level-6	0 (0)
Level-7	1 (0.9)
Expectedness	
Expected	109 (99.1)
Unexpected	1(0.9)
Preventability	
Non-Preventable	84 (76.3)
Possibly-Preventable	23 (20.9)
Preventable	3 (2.7)
Outcome	
Fatal	1 (0.9)
Not recovered / Not resolved / Ongoing	1 (0.9)
Recovered / Resolved	49 (44.5)
Recovered / Resolved with sequelae	1 (0.9)
Recovering / Resolving	14 (12.7)
Unknown	44 (40)

Seriousness	
No	26 (23.6)
Yes	56 (50.9)
Unknown	28 (25.4)

Discussion:

The ICSR analysis regarding the gender of patients showed that there **were** more reports for **males' (**57.4**%)** than **females' (**42.6**%)**.

Age group analysis of the reports showed that 45-64 **(50.9%)** years was the major category in the reporting of the ADRs related to Favipiravir, followed by 18-44 years **(**32.4**%)**, followed by 65-74 **(**15.7**%).** Regarding the **reporter** qualification, pharmacist was the major contributors to the ADRs reporting process with **(**85.2**%)** and **(**14.8**%)** percent by other health **professionals**, this is mainly due to that pharmacists in hospital and centers are directly supervised by the Iraqi pharmacovigilance center with continuous training to the pharmacists responsible for the pharmacovigilance by the IPhVC. In general, pharmacists have a favorable attitude about reporting ADRs and accept that it is a part of their professional responsibilities.

Based on the findings of the SOC, the analysis of Adverse Drug Reactions (ADRs) distribution pertaining to Favipiravir indicated a prevalence of 57.4% in gastrointestinal disorders, 35.2% cardiac disorders, 13.3% investigations (lab test abnormalities), 3.7% nervous system disorders, 1.9% general disorders and conditions at the administration site; whereas, 0.9% musculoskeletal and connective tissue disorders, 0.9% respiratory, thoracic, and mediastinal disorders, and 0.9% surgical and medical procedures, vascular abnormalities (0.9%) and blood and lymphatic system illnesses (0.9%) were the most often reported ADRS. Azithromycin is the most suspected/interacting drug that used concomitantly with Favipiravir as shown in (Table 4), this concomitant use may be linked to the high incidence of Cardiac and GIT ADRs, since Azithromycin is highly linked to these ADRs [14].

In accordance with the process of evaluating the causation of adverse drugs reactions. The predominant categorization of adverse drug reactions (ADRs) was determined to be possible, with probable and unlikely classifications following suit. In the field of reasonable categorization, it is postulated that Adverse Drug Reactions (ADRs) can be induced by concomitant administration of other medications or may arise as a consequence of the underlying condition being targeted by the treatment.

According to Table 2, Level 2 severity accounts for (41.8%) of all adverse drug reactions, demonstrating that most ADRs do not require antidotes or medication and do not lengthen hospital stays, unlike level 4 severity, which accounts for (15.4%) of all ADRs.

The severity assessment's moderate category includes both levels 2 and 4. One ADR was fatal, and the reaction was brought on by bacterial infectious diseases that could have been causative. The majority of ADRs were not preventable, according to the analysis of preventability.

The outcome for Favipiravir ADRs was mostly recovered-resolved ADRs **(**44.5%**)** while data regarding ADRs outcome were missing in 40% (Table 2).

Indicating that non-serious ADRs were likely underreported and underestimated by healthcare practitioners. Whereas substantial ADRs were the focus of reporting to the National Pharmacovigilance Center, seriousness analysis found that 50.5% of ADRs were severe.

Ankara, Turkey's "Atatürk Chest Diseases and Chest Surgery Training and Research Hospital" did a retrospective study. A study by (Ergür, Figen ztürk et al.), which comprised 357 patients who finished their

Favipiravir medication at the suggested dose, found that 37 (10.36%) of these individuals experienced side effects. In 26 (7.28%) of the individuals, liver dysfunction was the most frequent adverse event. Additionally, thrombocytopenia (0.28%), nausea (0.84%), diarrhea (1.4%), and abdominal pain (0.28%) were noted. One patient (0.28%) had nausea as well as elevated transaminases [15].

Compared to our study, there wasn't any reports with liver dysfunction, but 14 patients (13%) were reported to have high hepatic enzymes. The incidence of GIT ADRs was much higher in our study. Only one patient reported to has blood and lymphatic system disorders in both studies, but in our study the mentioned side effect was anemia, and in the other mentioned study the side effect was thrombocytopenia. Concomitant drugs used in both studies have huge effect on the results of both studies, since most of COVID-19 patients was managed but multi-drug regimen.

Study limitations:

The primary issue with the study was that the majority of data reports from the medical staff was lacked . The primary issue with the study was that the majority of data They deal with the patient's past, the length and amount of the medication taken, the patient's coexisting illness, and any further pharmacological therapies applied.

Conclusion and recommendations:

Favipiravir exhibits a diverse array of adverse effects, primarily impacting the gastrointestinal, cardiac, and nervous systems. These side effects encompass a spectrum of severity, ranging from expected and mild to more severe manifestations.

Greater emphasis should be placed on the recognition and mitigation of side effects to ensure effective treatment and prevention. Furthermore, it is imperative that healthcare establishments maintain a constant awareness of the significance of pharmacovigilance. Moreover, the personnel responsible for overseeing these establishments must undergo appropriate professional training to guarantee the precision of reported data and its effective analysis, ultimately leading to improved health outcomes. Furthermore, it is imperative to ensure that patients are adequately educated of the possible adverse reactions associated with their prescribed medications, as well as the appropriate procedures for reporting any such bad effects, should they occur.

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