Analysis of Azithromycin adverse events in COVID-19 Patients reported to Iraqi Pharmacovigilance center in 2020

Yasir A. Noori*,Inam S. Arif, Manal M. Younus***, Mohammed M. Mohammed***
***Department of Clinical Pharmacy, College of Pharmacy, Mustansiriyah University**
****Dean Assistant for scientific affairs, College of Pharmacy, Mustansiriyah University**
*****Iraqi Pharmacovigilance Center, Ministry of Health, Baghdad, Iraq**

Article Info:

Received Jun 2022
Accepted Sept 2022
Corresponding Author email:
pharm.dr.isamalhaj@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0002-1205-4829

DOI:

Abstract:

Azithromycin is an antibiotic that belongs to the macrolide family used in a wide variety of bacterial diseases. However, it has been proposed as a potential therapy for the treatment of SARS-CoV-2 pneumonia (off-label use) given for its antiviral and immunomodulatory activity. Never-theless, its role in the treatment of COVID-19 remains unclear. Azithromycin has a well-characterized safety profile. However, its use outside the approved indication needs further follow up to ensure that the benefit-risk balance remains positive. One method to look for new/ changed safety information is through using the information component (IC025) value. IC025 is the lower limit of a 95% credibility interval for the IC. The credibility interval provides information about the stability of a particular IC value: the narrower the interval, the higher the stability.

Objective:
Study the submitted adverse events reports of Azithromycin to the Iraqi Pharmacovigilance center and compare the occurrence of these reported adverse events in Iraq to the internationally reported cases during 2020COVID-19 pandemic using IC025.

Methodology:
The reported adverse events of Azithromycin to the national Pharmacovigilance database were studied qualitatively (age, gender and seriousness) and quantitatively (using IC025) as a measure of presence of a new/changed safety information related to Azithromycin.

Results:
The total number of reports for Azithromycin were 419, female represent (43%) and male represent (55.8%), and the predominant age groups was from 45-64 years representing (41.1%). The most widely reported adverse events were gastrointestinal disorders (68%), cardiac disorders (14.1%), general disorders and administration site effect (6.9%), and investigations (Interfere with Lab tests) (5.7%). There were 96 drug-adverse reaction combinations. The IC025 value for the most widely reported adverse events showed a comparable value for ECG-QT prolonged (3.6/3.7), Arrhythmia (0.6/0.7). There was a decreased value for palpitation (0.5/0.9) and dyspnea (0.3/0.6). Tachycardia and increased liver enzymes showed an increased value of (2.0/0.1) and (0.5/0.1) respectively.

Conclusion:
Using the IC025 was helpful in finding the increased reporting rate of adverse events compared to the background rate.

Key words: Corona Virus, Covid-19, Azithromycin, Pharmacovigilance, Adverse events.

تحليل الأحداث الضائرة لأزيثروميسين لدى مرضى كوفيد -19 التي تم الابلاغ عنها إلى المركز العراقي لليقظة الدوائية في عام 2020.

ياسر عز الدين نوري*, انعام سامح عارف, منال محمد يونس***, محمد محمود محمد*.**
قسم الصيدلة السريرية ، كلية الصيدلة ، الجامعة المستنصرية
مساعد العميد للشؤون العلمية ـ كلية الصيدلة ـ الجامعة المستنصرية
المركز العراقي لليقظة الدوائية ، وزارة الصحة ، بغداد ، العراق

الخلاصة:

أزيثروميسين هو مضاد حيوي ينتمي إلى عائلة الماكرولايد المستخدمة في مجموعة واسعة من الأمراض البكتيرية. ومع ذلك ، فقد تم اقتراحه كعلاج محتمل لعلاج الالتهاب الرئوي SARS-CoV-2 (استخدام بدون تصريح) نظرًا لنشاطه المضاد للفيروسات وتأثيراته على المناعة. ورغم ذلك ، لا يزال دوره في علاج COVID-19 غير واضح. أزيثروميسين لديه ملف أمان جيد المواصفات. ومع ذلك ، فإن استخدامه خارج الاستعمال المعتمد يحتاج إلى مزيد من المتابعة للتأكد من أن توازن الفوائد والمخاطر يظل إيجابيًا. تتمثل إحدى طرق البحث عن معلومات الأمان الجديدة / المتغيرة في استخدام قيمة مكون المعلومات IC025 (IC025). هو الحد الأدنى من فاصل المصداقية 95٪ لـ IC. يوفر فاصل المصداقية معلومات حول استقرار قيمة IC معينة: كلما كان الفاصل الزمني أضيق ، زاد الاستقرار.

الهدف من الدر اسة:

دراسة تقارير الأحداث السلبية المقدمة عن أزيثروميسين إلى المركز العراقي لليقظة الدوائية ومقارنة حدوث هذه الأحداث الضارة المبلغ عنها في العراق بالحالات المبلغ عنها دوليًا خلال جائحة كوفيد-19 لعام 2020 باستخدامIC025

المنهجية:

تمت دراسة الأحداث الضارة المبلغ عنها لأزيثروميسين لقاعدة البيانات الوطنية لليقظة الدوائية نوعيًا (العمر والجنس والخطورة) وكميًا (باستخدام IC025 كمقياس لوجود معلومات سلامة جديدة / متغيرة تتعلق بأزيثروميسين

النتائج:

بلغ العدد الإجمالي للتقارير عن أزيترومايسين 419، للإناث 43٪ والذكور 55.8٪، والفئات العمرية السائدة كانت من 45-64 سنة بنسبة 41.1٪. كانت الأحداث الضارة الأكثر انتشارًا هي اضطرابات الجهاز الهضمي 68٪، واضطرابات القلب 14.1٪، والاضطرابات العامة وموقع الإعطاء 6.9٪ ، والتداخل مع التحاليل المختبرية 5.7٪. كان هناك 96 مجموعة من التفاعلات العكسية للأدوية. أظهرت قيمة IC025 للأحداث الضارة التي تم الإبلاغ عنها على نطاق واسع قيمة قابلة للمقارنة لـ ECG-QT لفترات طويلة (3.6 / 3.7) ، عدم انتظام ضربات القلب (0.6 / 0.7). كان هناك انخفاض في قيمة الخفقان (0.5 / 0.9) وضيق التنفس (0.3 / 0.6). تسارع القلب وزيادة إنزيمات الكبد أظهرت زيادة في القيمة (2.0 / 0.1) و (0.5 / 0.1) على التوالي.

الأستنتاج:

كان استخدام IC025 مفيدًا في إيجاد معدل الإبلاغ المتزايد عن الأحداث الضارة مقارنة بالمعدلات المتوقعة.

الكلمات المفتاحية: فيروس كورونا, ازيثروميسين, اليقظة الدوائية, الاثار الجانبية.

Introduction

Coronaviruses are important human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by a global pandemic. In February 2020, the World Health Organization (WHO) designated the disease COVID-19, which stands for coronavirus disease 2019 [1]. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2].

An international survey among physicians involved in the treatment of COVID-19 patients on antibiotic prescribing practices conducted in April 2020 revealed that the decision on antibiotic use was mostly based on clinical presentation, with the need for coverage of atypical pathogens and more than half of the participants reported use of a combination of β-lactams and macrolides or fluoroquinolones [3].

COVID-19-associated pneumonia has been shown to exacerbate the inflammatory

response of its host, which may exhibit a syndrome of systemic hyper-inflammation designated as a cytokine storm, and since cytokine storm, also known as cytokine release syndrome (CRS), seems to be a major driver of mortality in COVID-19, drugs with immunomodulation activity have been proposed as potential agents to be repurposed for the treatment of COVID-19 patients [4, 5].

There is currently great interest in drug repurposing or repositioning to manage COVID-19 infection, that is, the evaluation of the usefulness of a drug for an indication different to that for which it was marketed. One such case is the use of the antibacterial macrolide Azithromycin; it has been shown that Azithromycin has antiviral and immunomodulation properties [6].

The mechanisms of the antiviral effect of Azithromycin support a large-spectrum antiviral activity. It appears to decrease the virus entry into cells [7]. In addition, it can enhance the immune response against viruses by up-regulates the production of type I and III interferon (especially interferon-β and interferon-λ) [8].

The immunomodulation properties of Azithromycin are the rationale of its use against inflammatory manifestations leading to interstitial lung disease [9]. Azithromycin shows an immunomodulatory profile by inhibiting several cytokines involved in COVID-19 associated cytokine storm. Indeed, Azithromycin regulates and/or decreases the production of IL-1β, IL-6, IL-8, IL-10, IL-12, and IFN-α [10].

The goal of this study is to assess the adverse events associated with Azithromycin use (alone or concomitantly with other drugs) in COVID-19 patients in Iraq and compare it internationally for the detection of any new/changed safety information related to Azithromycin.

Methods:

This was a descriptive assessment of Azithromycin and its potential adverse events during its use in COVID-19 pandemic in 2020, based on data from VigiBase, the world's largest database of more than 20 million individual case safety reports (ICSRs) submitted by members of the WHO Program for International Drug Monitoring since 1968, and the risk of multiple adverse events occurring at the same time. This database is created and maintained by the Uppsala Surveillance Center (UMC) in Sweden.

VigiLyze was used to retrieve the reaction outcome, disproportionality measure (information component – IC_{025} value), and other relevant variables. VigiLyze is a data mining and analytics tool developed for VigiBase.

The information component (IC) is a measure of the disproportionality between the observed and the expected reporting of a drug-adverse event pair. A positive IC value indicates that a particular drug-adverse event pair is reported more often than expected, based on all the reports in the database. Conversely, a negative IC value means that the drug-adverse event pair is reported less frequently than expected. The higher the value of the IC, the more drug-adverse event pair is to be very noticeable. The IC025 value is the lower limit of a 95% credibility interval for the IC. The credibility interval provides information about the stability of a particular IC value: the narrower the interval, the higher the stability [11].

In the present study, we included all adverse events with high IC values that appear as (Iraqi IC_{025}/Global IC_{025} > 1), which can be defined as “a traditional threshold that indicates a correlation between drug-adverse reaction combination more than expected globally based on all reported cases found in VigiBase.

The seriousness of the adverse drug reaction (ADR) was ranked using the International Conference on Harmonization (ICH) E2A guideline (ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). As defined by the guideline, a

serious event or reaction is any untoward medical occurrence that at any dose: "(1) resulted in death; (2) is life-threatening; (3) required hospitalisation or resulted in prolongation of existing hospitalisation; (4) resulted in persistent or significant disability/incapacity, or (5) caused congenital anomaly/birth defect or medically important event or reaction that required medical/surgical intervention to prevent serious outcome" [12].

Exclusion Criteria:

Includes all adverse events that have the same or lower IC value compared to that globally found in VigiBase.

Result and Discussion:

The Iraqi Pharmacovigilance Center has assessed and documented 419 cases of adverse events regarding Azithromycin use in VigiBase over 2020 in COVID-19 pandemic, all instance are qualitatively screened, 180 reports for females (43%), 234 reports for males (55.8%), age group of affected patients range from 18 to 75 years of age as shown in **(table 1)**, regarding seriousness assessment, 178 reports was serious (42.5%), 241 reports non serious (57.5%), regarding fatality assessment, 4 reports of fatal cases in 2020 (1%).

Table (1): Reported age groups affected with Azithromycin adverse events

Patient age	Count	Percentage
28 days to 23 months	1	0.2
2 - 11 years	5	1.2
12 - 17 years	5	1.2
18 - 44 years	151	36.0
45 - 64 years	172	41.1
65 - 74 years	52	12.4
≥ 75 years	19	4.5
Unknown	14	3.3

The more co-reported active ingredients with Azithromycin are Hydroxychloroquine 45 reports (10.7%), Favipiravir 45 reports (10.7%), Oseltamivir 25 reports (6%), enoxaparin 15 reports (3.6%), paracetamol 11 reports (2.6 %), ceftriaxone 9 reports (2.1%), zinc 3reports (0.7%), cholecalciferol 3 reports (0.7%), Ascorbic acid one report (0.2%) and Bromhexine one report (0.2%). The most Reported ADRs are presented in (table 2).

Table (2): The most reported adverse drug reactions (ADRs)

Adverse drug reaction	No. of reports	Percentage
gastrointestinal disorders	285	(68%)
cardiac disorders	59	(14.1%)
general disorders and administration site	29	(6.9%)
Investigations (Interfere with Lab test)	24	(5.7%)

Regarding quantitative analysis of Iraqi database, for patients who used Azithromycin in a variety of dosage forms, 96 combinations containing 505 adverse

drug reactions (ADRs) were gathered over the 2020 by the Iraqi Pharmacovigilance Center. There were 24 cases of prolonged QT interval, 154 cases of Upper abdominal pain, 52 cases of tachycardia, 122 cases of diarrhoea, 30 cases of constipation and 22 cases of abdominal discomfort. Many adverse effects, including tachycardia, Upper abdominal pain, constipation, and prolonged QT interval, are more common in Iraqi records than in internationally known instances. Seriousness assessment of these reactions was (32%) of ADR was serious. (Table 3) compare the Iraqi IC025/Global IC025 ratio, gender, seriousness, patient age, concurrent drug use and multiple adverse drug reactions among the most common adverse drug reactions stated in the summary of product features.

The IC025 value for the most widely reported adverse events showed a comparable value for ECG-QT prolonged (3.6/3.7), Arrhythmia (0.6/0.7) which means that the reported adverse events in Iraq have the same expected value, which is globally based on all reported cases found in VigiBase. There was a decreased value for palpitation (0.5/0.9) and dyspnea (0.3/0.6), which means that the adverse events are reported less frequently in Iraqi patients compared to the global reports. Tachycardia and increased liver enzymes showed an increased value of (2.0/0.1) and (0.5/0.1) respectively, which means that the adverse events are reported more frequently in Iraqi patients compared to the global reports.

According to (Zhao, Y, et al. 2022) in 2020, 312 of the 575 reports of serious cardiovascular adverse events (SCAEs) listed concomitant use of Hydroxychloroquine/chloroquine (HCQ/CQ) and azithromycin, including QTc prolongation (61.4%), Ventricular tachycardia (12.0%), atrial fibrillation (8.2%), and cardiac arrest (4.4%).[13]. In comparison with our study, the percentage of QTc prolongation was significantly higher in this study, slightly higher percentage of Ventricular tachycardia in this study compared to ours and an even percentage of cardiac arrest. In case of atrial fibrillation, the adverse event was not mentioned in the VigiBase, but it is considered as a type of Tachycardia or Arrhythmia, so it is not possible to compare it with our classification although the percentage of Tachycardia and Arrhythmiatogether is about (13.8%) in our study, which is comparable to the percentage mentioned in this study.

Table (3): The most common adverse drug reactions of Azithromycin reported to the Iraqi Pharmacovigilance Center

ADR	Case (No.)	IC_{025} Iraq/IC_{025} Global	Gender No. (%)	Dominant age group	Seriousness No. (%)	Concomitant Drugs
ECG-prolonged QT interval	24	3.7/3.6	M 18 (75) F 6 (25)	45-64yr. 33.3%	20 (83.3)	50% Hydroxychloroquine 4.2% Oseltamivir
Upper abdominal pain	154	3.6/1	M 82 (53.2) F 71 (46.1) U 1 (0.6)	45-64yr. 43.5%	8 (5.2)	2.6% Hydroxychloroquine 1.9% Ceftriaxone 1.9% Favipiravir
Tachycardia	52	2/0.1	M 22 (42.3) F 28 (53.8) U 2 (3.8)	45-64yr. 44.2%	41 (78.8)	53.8% Favipiravir 7.7% Paracetamol
Diarrhoea	122	1.8/1.6	M 68 (55.7) F 50 (41) U 4 (3.3)	45-64yr. 34.4%	31 (25.4)	6.6% Favipiravir 3.3% Enoxaparin
Constipation	30	1.7/-0.7	M 17 (56.7) F 13 (43.3)	45-64yr. 53.3%	24 (80)	43.3% Favipiravir 6.7% Enoxaparin 6.7% Dexamethasone
Abdominal Discomfort	22	1.6/1.4	M 11 (50) F 7 (31.6) U 4 (16.2)	45-64yr. 63.6%	0 (0)	9.1% Bromhexine 4.5% Zinc 4.5% ASA
Arrhythmia	6	0.7/0.6	M 4 (66.7) F 2 (33.3)	45-64yr. 66.7%	4 (66.7%)	33.3% Oseltamivir 16.7% Chlorpromazine 16.7% Hydroxychloroquine
Palpitation	13	0.5/0.9	M 7 (53.8) F 6 (46.2)	18-44yr. 38.5% 45-64yr. 38.5%	1 (7.7)	30.8% Hydroxychloroquine 7.7% Salbutamol 7.7% Zinc
Increased Hepatic enzyme	6	0.5/-0.1	M 4 (66.7) F 2 (33.3)	18-44yr. 50%	1 (16.7)	16.7% Hydroxychloroquine 16.7% Diazepam 16.7% Paracetamol
Nausea	69	0.4/0.7	M 35 (50.7) F 34 (49.3)	45-64yr. 40.6%	33 (47.8)	11.6% Oseltamivir 1.4% Zinc 1.4% ASA
Dyspepsia	7	0.3/0.6	M 4 (57.1) F 3 (42.9)	45-64yr. 57.1%	0 (0)	14.3% Oseltamivir 14.3% Hydroxychloroquine

ADR: Adverse drug reaction, M: Male, F: Female, U: Unknown, ECG: electrocardiogram, ASA: Acetylsalicylic Acid (Aspirin), yr.: Years, IC: Information Component

Limitations of the study:

The major limitation of the study was missing information in most of the reports by the healthcare workers, which is related to the history of the patient and the duration and dose of the drug used, alongside the concomitant medical condition of the patient and other pharmacological treatments involved.

Conclusion:

The cases reported to the Iraqi Pharmacovigilance center include several concurrent drug usages, making it a challenge to determine whether Azithromycin is to blame for these side effects. According to the global data of the WHO, the majority of those effects have small difference between their percentages, and some of them show negative correlations, which indicates that the expected reports are higher than those actually reported. Some of the adverse effects reported showed a great difference in IC025 between cases reported in Iraq and those globally recorded as in Upper abdominal pain, tachycardia, constipation and increased hepatic enzyme. It rarely affects their usage, but this side effect may affect patient adherence.

References:

1- Tedros A. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020.

2- Nitulescu GM, Paunescu H, Moschos SA, Petrakis D, Nitulescu G, Ion GND, Spandidos DA, Nikolouzakis TK, Drakoulis N, Tsatsakis A. Comprehensive analysis of drugs to treat SARS-CoV-2 infection: Mechanistic insights into current COVID-19 therapies (Review). Int J Mol Med. 2020 Aug; 46(2):467-488.

3- Rawson TM, Ming D, Ahmad R, Moore LSP, Holmes AH. Antimicrobial use, drug-resistant infections and COVID-19. Nat Rev Microbiol. 2020;18: 409–10.

4- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395:497–506.

5- Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Investig. 2020; 130:2620–9.

6- Sultana J, Cutroneo PM, Crisafulli S, Puglisi G, Caramori G, Trifiro G. Azithromycin in COVID-19 Patients: Pharmacological Mechanism, Clinical Evidence and Prescribing Guidelines. Drug Saf. 2020;43: 691–8.

7- Tran DH, Sugamata R, Hirose T, Suzuki S, Noguchi Y, Sugawara A, et al. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza (H1N1) pdm09 virus infection by interfering with virus internalization process. J Antibiot (Tokyo). 2019; 72:759–68.

8- Andreani J, Le Bideau M, Duflot I, Jardot P, Rollanda C, Boxberger M, et al. In vitro testing of hydroxychloroquine and Azithromycin on SARS-CoV-2 shows synergistic effect. Microb Pathog. 2020;25(145):104228.

9- Kawamura K, Ichikado K, Suga M, Yoshioka M. Efficacy of Azithromycin for treatment of acute exacerbation of chronic fibrosing interstitial pneumonia: a prospective, open-label study with historical controls. Respiration. 2014; 87:478–84.

10- Cai M, Bonella F, Dai H, Sarria R, Guzman J, Costabel U. Macrolides inhibit cytokine production by alveolar macrophages in bronchiolitis obliterans organizing pneumonia. Immunobiology. 2013; 218:930–7.

11- Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, De Freitas RM. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998 Jun; 54(4):315-2
12- ICH Steering Committee. Clinical safety data management: definitions and standards for expedited reporting E2A. Accessed 22 Apr 2021.
13- Zhao, Y., Zhang, J., Zheng, K. et al. Serious Cardiovascular Adverse Events Associated with Hydroxychloroquine/Chloroquine Alone or with Azithromycin in Patients with COVID-19: A Pharmacovigilance Analysis of the FDA Adverse Event Reporting System (FAERS). Drugs - Real World Outcomes 9, 231–241 (2022).