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Evaluation of the Renal Safety of Direct Acting Antivirals in Chronic Hepatitis C Patients

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors contributed to the study conception and design. Material preparation, data collection and analysis both authors commented on the manuscript and revised it critically for important intellectual content. Author MS supervised this study. Both authors read and approved the final manuscript.

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ABSTRACT

Objective: Direct acting antivirals (DAA) is a class of antivirals that has been extensively used in chronic hepatitis C virus (HCV) patients over the past 6 years. Despite the excellent therapeutic benefits of DAA, there is a knowledge gap regarding the safety of this class. Several reports of possible renal toxicity associated with DAA administration can be found in the literature. The aims of this study are: to assess the renal safety of DAA used for the treatment of chronic HCV infection and to quantify the odds of developing renal toxicity in patients with chronic HCV viral infection.
Study Design: Disproportionality analysis was used to detect signals of potential side effects.
Place and Duration: Amman –Jordan, One year study since September 2017 to march 2018.
Methods: The method that was applied in the current study is obtaining the data from United States (US) food and drug administration (FDA) adverse event reporting system (FAERS). Data between July, 2014 and September, 2017 were combined and explored. Disproportionality analysis was conducted to reports from chronic HCV patients to explore possible association between DAA administration and renal side effects.

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Results: This study showed that a total of 3,837,418 safety reports were available in the period between July, 2014 and September, 2017. Patients with chronic HCV infection represent 22,022 cases. When considering all DAA as drug of interest, the use of DAA alone or in combination with interferon and/or ribavirin did not increase the risk of having renal side effects. Exploring individual DAA demonstrated a significant association between the incidence of renal side effects and the administration of telaprevir and dasabuvir. Considering renal side effects individually showed a significant association between DAA administration and chronic kidney disease.
Conclusions: In this study, we reported a significant association between DAA administration and chronic kidney disease and between telaprevir or dasabuvir and renal side effect. These findings are used for hypothesis generation rather than testing.

Keywords: Adverse drug reactions reporting systems; pharmacovigilance; hepatitis C; direct acting antiviral.

1. INTRODUCTION

Hepatitis C is a disease that is characterized by inflammation of the liver caused by hepatitis C virus (HCV). It is blood borne disease that is transferred by blood from one person to another. This might happen through injection drug users, unsafe injection practice, unsafe health care, and transfusion of unscreened blood and blood products [1]. Hepatitis C might be chronic or acute illness ranging from mild that last for few weeks to chronic disease that is a lifelong disease [2].

The goal of therapy is to slow the progression of the disease, slow development of cirrhosis, and other liver injury. Once patient is diagnosed with HCV treatment should be initiated to decrease mortality and morbidity [3].

In general, treatment is safe and effective. Most treatment regimens are for 2-3 months. Effectiveness of therapy is measured by sustained virologic response (SVR). SVR is not detecting HCV for 12 weeks after completion of therapy [3]. Factors to consider before beginning a regimen are liver condition of patient, genotype of HCV, and presence of other illness such as kidney disease or liver transplant [4].

There are three main groups that used in treatment of HCV infection. Interferon based therapy was considered a cornerstone in treatment of HCV. Interferon based therapy has a high cure rate, affordable cost. Interferon is routinely used in combination with ribavirin to improve cure rate.

DAA are new group that is currently considered the drug of choice for the treatment of chronic HCV infection. DAA therapy results in a cure rate of more than 90% with low incidence of side effects. The high cost is a main limitation toward using DAA for HCV infection [5].

The approvals of DAA, such as simeprevir and sofosbuvir, for the treatment of chronic HCV infection is supported by clinical evidence from multiple trials [6].

These approvals have improved the chances of virologic cure with a shorter duration of treatment; possibly fewer adverse events; and the option of all oral, interferon-free treatment for chronic HCV infection. Sofosbuvir and/or simeprevir are now a component of all standard-of-care regimens in multiple sets of latest published guidelines [6,7].

Despite the high efficacy of DAA, several adverse events were associated with DAA use. Most of these adverse events are mild and does not require changing antiviral treatment regimen. Examples of mild adverse events include fatigue, headache, nausea, diarrhea, and dizziness [8,9,10] Skin problems has been reported such as photosensitivity and rash [10] More severe complications include anemia, portal vein thrombosis, streptococcus bacteremia, and pneumonia [8,10].

Several researchers reported an abrupt increase in hepatitis B viral load in chronic HCV patient receiving DAA therapy [11]. Hepatitis B reactivation is common in immunocompromised patients such as: HIV patients [12], autoimmune disease patients [13], and patients receiving immunosuppressant therapy [13]. Hepatitis B reactivation may lead to severe complications such as liver failure and death [14].

One case report has been associated with sofosbuvir and daclatasvir causing acute interstitial nephritis [15]. Kidney injury has been also reported in patients receiving ledipasvir with

sofosbuvir combination therapy [16]. **'**Despite these two case reports, there is a knowledge gap regarding the renal safety of DDA' there are data in the literature, however, it is limited and requires further confirmation.

Adverse drug reaction [17] for drug underdevelopment and before it is approval can be detected, prevented, and minimized. Rare and long term adverse drug reaction are difficult to detect during drug development stages. It is only possible to identify them when the drug begin to be used by large population after marketing authorization [18].

Self-reporting system considered as most important source of data used in pharmacovigilance because of its usefulness and availability of information. It is mainly responsibility of health care professionals, consumers, and pharmaceutical companies. It protects patient from harm during drug post marketing period. In US, pharmacist is considered as most important health care provider in spontaneous adverse drug reaction reporting [19].

Each report includes one or more adverse events that are associated with the drug, indication and limited demographic information. All of these reports are available in FDA website. They are grouped to quarters, each quarter contains files of different information [20].

The major aim of pharmacovigilance is signal detection. To detect unknown association between drug and unexpected event. Signal detection can be calculated or extracted from different disproportional analysis. It consist of a hypothesis together with data and argument, argument in favor or against hypothesis [21].

The WHO has setup an international program for adverse drug reaction monitoring. This program has an important role in drug safety monitoring. Other health authorization, such as European medicine agency (EMA) and US food and drug administration (FDA) have collaborated to improve pharmacovigilance, share the information, and spread safety awareness worldwide [22].

1.1 Importance of the Study

The objective of the present work is to assess the renal safety of DAA in patients with chronic HCV infection. All DAA were approved for the treatment of chronic HCV infection after 2010. The safety profile is not completely established when compared to older medication like interferons that were used for more than 25 years.

Safety data obtained from US-FDA adverse event reporting system (FAERS) were analyzed. FAERS provides access to huge datasets that contains more than 5,000,000 reported case between years 2004 and 2017. The availability of such source maximizes the odds of identifying rare side effects such as renal toxicity.

2. METHODOLOGY

2.1 Pharmacovigilance Data Mining

2.1.1 Data source

Data included in the present analysis were obtained from the FAERS. FAERS is the largest database for spontaneous report. FAERS contains reports submitted to FDA by health professionals and consumers. Data were downloaded from the following website:

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm

2.1.2 Data description

The FDA publish summary of submitted safety reports and makes them available to the public. FAERS database contains safety reports for a given year divided into four quarters: Jan-March, April-June, July-September, and October-December. We included safety reports for the period of July 2014 to September 2017. Each quarter contains seven data files .These files could be formatted either as XML or ASCII. The seven data files are:

1) Demographic file (DEMO): it contains patient demographic and administrative information.
2) Drug file (DRUG): it contains drug/biologic information for as many medications as were reported for the event.
3) Reaction file (REAC): it includes all adverse drug reactions coded by Medical Dictionary for Regulatory Activities (MedDRA) terminology.
4) Outcome file (OUTC): it contains type of outcome such as death, life-threatening condition, and hospitalization.
5) Report source file (RPSR): it contains report source for the report.

6) Therapy file (THER): it contains drug therapy start dates and end dates for the reported drugs.
7) Indication file (INDI): it contains all Medical Dictionary for Regulatory Activities (MedDRA) terms coded for the indications of use for the reported drugs

Each file can be linked to other files using identifying number named "PRIMARYID" as a primary key field. The PRIMARYID is a seven digits number that exclusively identifies FAERS reports and allows cross-mapping all data files.

One more important field is "CASEID" classifying a FAERS case. CASEID number may include more than one report (PRIMARYIDs) owing to the possible follow-up of the same drug reaction. The duplicate PRIMARYIDs will have the same CASE number. Hence, it is important to make sure that the CASEID is correctly linked to the PRIMARYID.

2.1.3 Report inclusion criteria

Safety reports of patients with "chronic hepatitis C" were included in this analysis. We explored cases included the latest two quarters of 2014, four quarters of 2015 and 2016, and the first three quarters of 2017.

2.1.4 Report exclusion criteria

1) Safety Report with ambiguous drug names such as generic DAA
2) Cases of Chronic hepatitis C virus as an outcome.
3) Reports with missing indication.
4) If the adverse event has resulted from drug fetal exposure.
5) Duplicate reports with similar case ID

2.1.5 Data mining process

Data mining involves data cleaning, combining files from different quarters, select patients with chronic HCV, and data organization. Data mining allows the application of statistical techniques for quantitative signal detection. A pharmacovigilance signal consists of a hypothesis together with data and arguments, arguments in favor and against the hypothesis.

1. Data compilation

In the present analysis, we included data from the following file types: DEMO, DRUG, REAC, OUTC, THER, and INDI. For each file type, files from different quarters of years 2014-2017 were combined into a single file. Data compilation was performed using R software (version 3.4.2)

2. Identification of side effects reported in hepatitis C patients

Reports from patients with chronic hepatitis C were selected from indications file. The selection was based on Case ID.

3. Identification of side effects caused by antiviral drugs

Chronic hepatitis C patients receiving various - antiviral medications were grouped into several groups base on medications used. These groups are: patients receiving DAA without interferon or ribavirin, patients receiving interferon or ribavirin without DAA, and patients receiving DAA therapy with interferon or ribavirin. Only reports where the antiviral was considered as "interacting", "primary suspect", or "secondary suspect" drug will be selected.

4. Identification of cases with drug induced renal toxicity

Pharmacovigilance reports that include renal side effects were selected by cross- mapping PT with a list of renal side effects. The list is presented in Table 1.

2.2 Statistical Data Analysis

Disproportionality analysis was used to detect signals of potential side effects. Disproportionality analysis include the estimation of various reporting ratios for the incidence of the side effect of interest and compare to the incidence of other side effects by the same drug or the same side effects reported for other drugs. In order to perform disproportionality analysis, a contingency table needs to be constructed using pharmacovigilance database (Table 2).

In this study, we used the following measures of Disproportionality statistics:

1. Proportional reporting ratio (PRR)

$$PRR = \frac{A/(A+B)}{C/(C+D)}$$

Table 1. List of renal side effects

• Acute kidney injury	• Hemodialysis
• Anuria	• Kidney hypermobility
• Bladder dilatation	• Kidney transplant rejection
• Blood creatinine increased	• Nephrolithiasis
• Chronic kidney disease	• Proteinuria
• Complications of transplanted kidney	• Pyelonephritis acute
• Bacterial cystitis	• Renal abscess
• Dysuria	• Renal cell carcinoma
• Abnormal Glomerular filtration rate	• Renal cyst
• Decreased Glomerular filtration rate	• Renal failure
• Increased Glomerular filtration rate	• Renal impairment
• Glomerulonephritis	• Urinary bladder hemorrhage
• Acute Glomerulonephritis	• Urinary incontinence
• Hematuria	• Urinary tract infection

Table 2. Formal 2x2 contingency table that summarizes adverse events

	Direct Antiviraldrug	All other drugs	Total
Renal adverseeffects	A	B	A+B
All other adverseeffects	C	D	C+D
Total	A+C	B+D	A+B+C+D

PRR is calculated according to the following equation:

The 95% confidence interval (CI) of PRR is calculated according to the following:

$$95\%CI = EXP\left[Ln(PRR) \pm 1.96\sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}\right]$$

2. Reporting Odd Ratio (ROR)

ROR is calculated according to the following equation:

$$ROR = \frac{A/C}{B/D}$$

3. Chi squared statistic

Chi squared statistic with Yates correction was used to test for independence in the contingency table (Table2).

These calculations were done using R-Software and OpenVigil tool (available at http://openvigil.sourceforge.net/).

2.3 Criteria to Identify Pharmacovigilance Signal

In order to consider association between drug exposure and side effect a statistically significant signal the following criteria must be meet:

1. A PRR value of more than 2
2. A number of cases of 3 or more
3. A chi squared statistic of more than 4

2.4 Statistical Program

Data manipulation and statistical computations were done using R software (version 3.4.2; http://cran.r-project.org). Additionally, odds ratio and chi-square were computed using.

Online Pharmacovigilance tool available at http://openvigil.sourceforge.net/

3. RESULTS

3.1 Demographics

In order to extract information about the reporter from July 2014 to September 2017, demographic files that include demographic information like

gender, reporter's information, and countries, were used and analyzed.

3.2 Reports Based on Country

Summary of reporting countries for reports in chronic HCV patients is presented in and Fig. 1. This table was generated by summarizing DEMO file for patients with HCV infection. More than 50% of the reports were generated from the United States (n= 11833, 54%). Japan reported 3,597 reports that accounts for 16% of all reports. European countries that include Italy, Germany, France, Spain, and United Kingdom reported 14% of all reports. Reports from Canada and Egypt accounted for 3% and 1%, respectively, of all reports. Other countries reported around 7% of all reports. Reporter country was not available in 1,432 repots (~7%).

3.3 Reports by Year

Fig. 2 summaries reports by year. The year 2015 with period between January-December has the highest number of reports (N = 10052) report and the highest number of monthly reports (838 report/ month). Then year 2014 has the lowest number of reports (N = 1589) and monthly number of report equal to (265 report/month).

3.4 Gender

In more than half of all report the patient was male (n= 1483, 51%). Female patients constitutes 42% (n= 9257) of all patients. The gender was not available in 7% of all reports. More details are presented in and Fig. 3.

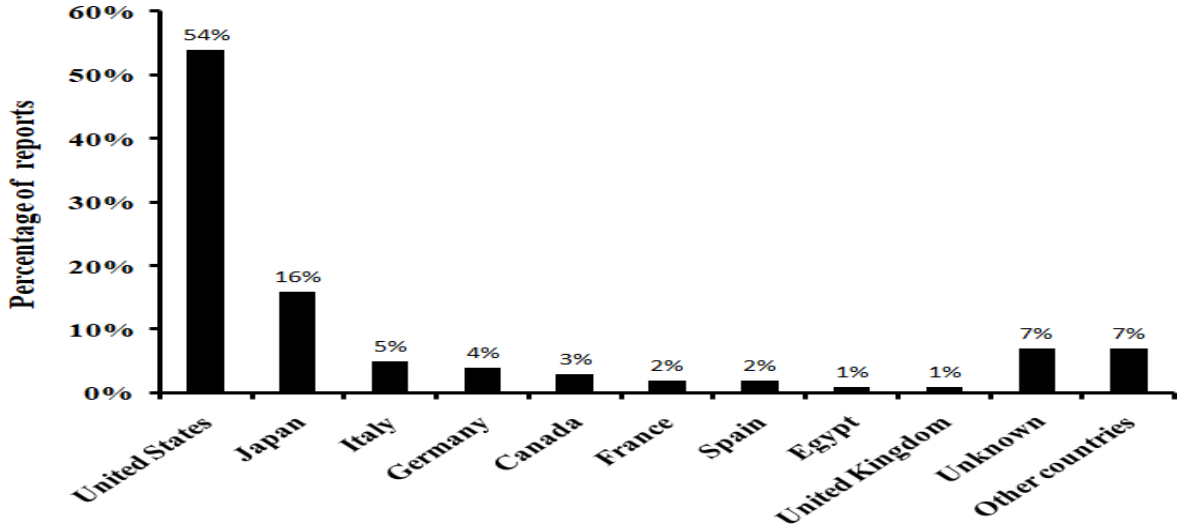

Fig. 1. Summary of reports by country

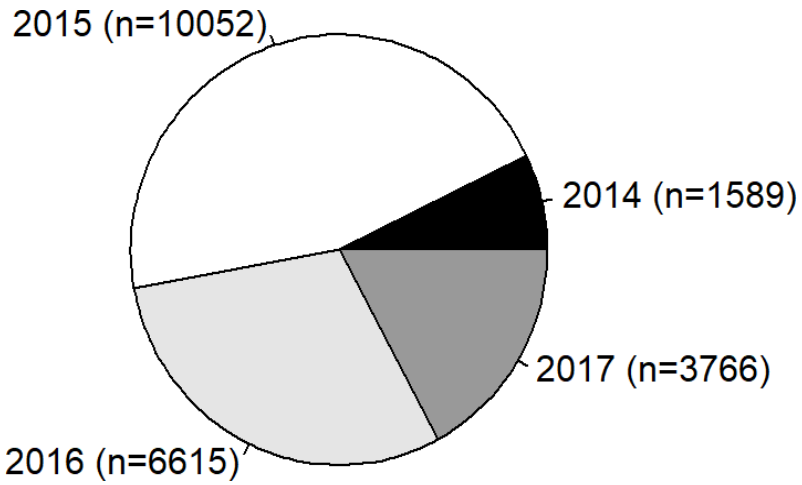

Fig. 2. Summary of reports by year

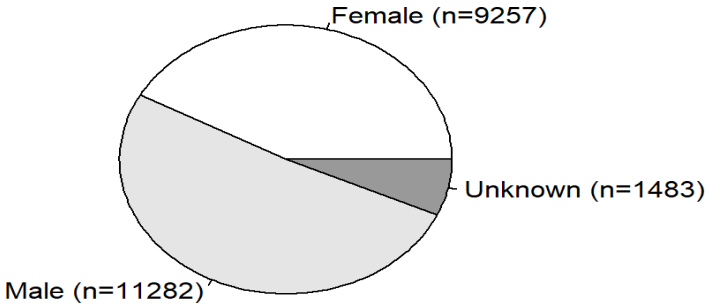

Fig. 3. Report distribution based on patient gender

3.5 Reporter's Occupation

The majority of cases were reported by consumers, with a percent of 41%, followed by physicians with a percent of 27%, health-professional other than physician and pharmacist with a percent of 21%, the pharmacists with a percent of 10%, and the least number of report cases reported by lawyers with a percent of.01%. Reporter occupation was not available in less than 1% of reports. Further details are displayed in Fig. 4.

3.6 Summary of Safety Reports

A total of 3,837,418 safety reports were available in the period between July, 2014 and September, 2017. Patients with chronic HCV infection represent 22,022 cases. About 5% (n=996) of cases reported in patients with chronic HCV infection were reports of renal side Effects.

Approximately 18% (n=183) of these reports were from patients that received DAA without interferon or ribavirin. Patients treated with interferon or ribavirin without DAA represent 14% (n=140) of the cases of renal side effects. The combination of DAA with interferon or ribavirin was observed in 37% (n=369) of the renal side effect cases. Patients treated with medications other than DAA, interferon, or ribavirin represent 31% (n=304) of cases with renal side effects. The remainder 21,026 cases represent cases of non-renal side effects. Majority of non-renal side effects (38%, n=7984) of the cases were reported in patients receiving a combination of DAA with interferon and/or ribavirin. DAA therapy without interferon or ribavirin was observed in about 14% (n=2849) of patients with non- renal side effects. Patients treated with interferon and/or ribavirin represent 21% (n=4420) of reports of non-renal side effects. About one quarter (27%, n=5773) of non-renal side effects cases were reported in patients receiving medications other than DAA, interferon, and ribavirin. The details are available in Fig. 5 and Table 3.

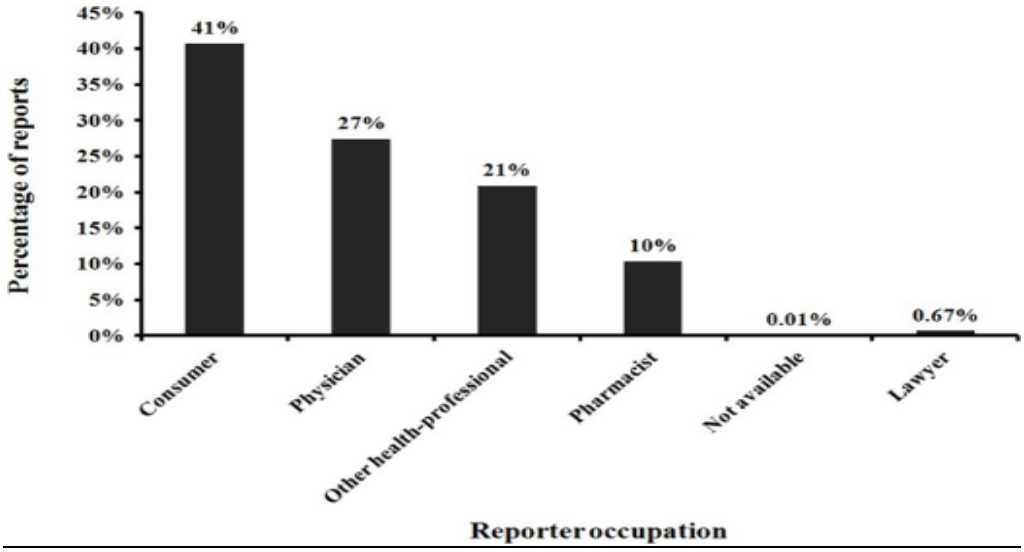

Fig. 4. Summary of reports based on reporter's occupation

Table 3. Summary of disproportionality analysis for directing acting antivirals(DAA) compared to other groups

Agents used in treatment of chronic hepatitis C	Renal side effects,n (%)	Non-renal side effects, n (%)	Total	PRR	ROR
DAA (without interferon orribavirin)	183 (18%)	2849 (14%)	3032	1.41	1.44
Interferon and/or ribavirin(without DAA)	140 (14%)	4420 (21%)	4560	0.63	0.61
DAA with interferon and/orribavirin	369 (37%)	7984 (38%)	8353	0.96	0.96
Other medications	304 (31%)	5773 (27%)	6077	1.15	1.16

** PRR: proportional reporting ratio, ROR: reporting odds ratio*

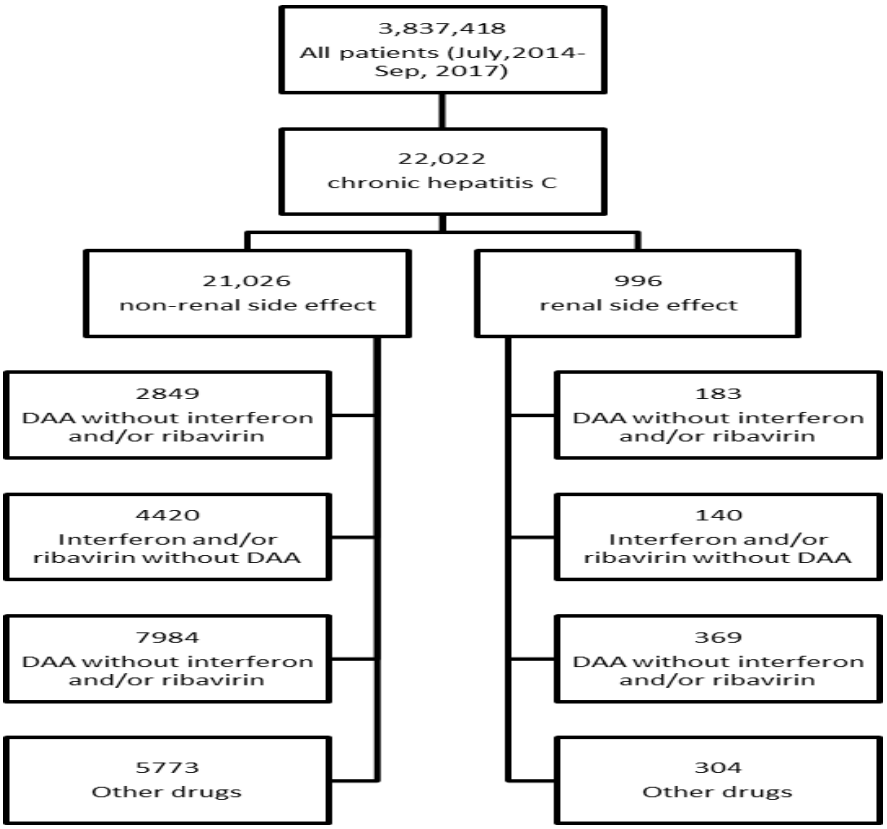

Fig. 5. Summary of safety reports distribution

3.7 Disproportionality Analysis

PRR and ROR for the incidence of renal side effects in chronic HCV patients are presented in Table 3. The PRR for the incidence renal side effects in patients treated with DAA without interferon and/or interferon is 1.41. ROR for the same treatment group was 1.44. Regarding patients treated with interferon and/or ribavirin without DAA, PRR and ROR were 0.63 and 0.61 respectively. PRR and ROR in patients treated with DAA with interferon and/or ribavirin were 0.96 and 0.96. Finally, PRR and ROR values for other treatment groups were 1.15 and 1.16.

Disproportionality analysis was also performed for each DAA agent individually. The highest PRR value of and ROR values were observed with Ombitasvir. Renal side effects signal (PRR>2) is detected in the following DAA: Ombitasvir, Boceprevir, Telaprevir, Paritaprevir, Ritonavir, Dasabuvir, Grazoprevir, and Elbasvir. A pharmacovigilance signal is based on a PRR value of more than 2 [23]. However, number of reports of renal side effects were ≥3 for the following DAA: Telaprevir, Ritonavir, Dasabuvir, Grazoprevir, and Elbasvir. No renal side effects were reported with Atazanavir, Ledipasvir, Adefovir dipivoxil, Velpatasvir, Entecavir, Tenofovir disoproxil fumarate, and Odalasvir.

Table 4 presents the frequency of various renal side effects. Most common renal side effect were reported is renal failure (N =121), followed by renal impairment (N = 117), Acute kidney injury (N = 112), Urinary tract infection (N = 86). Least common renal side effect is Glomerulonephritis acute, Complications of transplanted kidney, Kidney hypermobility , Glomerular filtration rate increased , Renal cell carcinoma , Renal abscess, Glomerular filtration rate abnormal with one case for each (N =1). In terms of PRR values, four renal side effects had a PRR value of more than 2: Chronic kidney disease, Hemodialysis, Cystitis Escherichia, and Complications of transplanted kidney. However, chronic kidney disease was the only renal side effects of number of reports of more than 3. Detailed Disproportionality analysis is provided in Table 5.

4. DISCUSSION

Pharmacovigilance signal detection enabled us to assess the renal safety of direct-acting antivirals in patients with chronic hepatitis C virus infection by analyzing the publicly available FAERS database. We also applied disproportionality analysis to estimate the odds of developing renal toxicity in patients with chronic HCV viral infection.

The use of DAA alone or in combination with interferon and/or ribavirin did not increase the risk of having renal side effects. Disproportionality analysis was also conducted to cases of patients receiving interferon and/or ribavirin. This was done to examine whether the change in the risk of renal disease is associated with chronic HCV infection or associated with DAA therapy [24]. Patients receiving interferon and/or ribavirin were used as a reference group. Even though PRR and ROR were more than 1 in patients receiving DAA without interferon or ribavirin, it is not considered statistically significant. A common threshold for the values of PRR and ROR is 2 in order to be a disproportionate signal [24,25].

Table 4. Frequency of different renal side effects in patients receiving direct acting antivirals (without interferon or ribavirin)

Side effect	N	PRR	Side effect	N	PRR
Renal impairment	41	1.90	hematuria	2	0.74
Renal failure	36	1.54	Nephrolithiasis	2	0.42
Acute kidney injury	33	1.22	Hemodialysis	2	6.26
increased Blood creatinine	31	1.78	acute Pyelonephritis	1	0.78
Urinary tract infection	24	1.17	Bacterial cystitis	1	6.26
Chronic kidney disease	11	4.59	Acute glomerulonephritis	1	NA
Dysuria	8	1.22	Complications of transplanted kidney	1	6.26
decreased Glomerular filtration rate	3	0.51	abnormal Glomerular filtration rate	1	NA

Table 5. Detailed Disproportionality analysis with chronic kidney disease as side effect of interest for direct acting antivirals(DAA) without interferon or ribavirin

Disproportionality indicators	Value	Interpretation
% of chronic kidney disease	0.36%	Percentage of chronic kidney disease vs all adverse events for DAA
Chi squared Yates (chisq)	15.5	Is there a statistical association between theChronic kidney disease and DAA? Values greater than 4 correspond to p<0.05.
Relative Reporting Ratio (RRR)	3.07	These ratios compare the observed counts to expected counts andallow to quantify the additional risk/odds of the drug and event selected above compared to the general background noise.
ortional Reporting Ratio (PRR) corresponds to Relative Risk	4.59	
Reporting Odds Ratio (ROR)	4.61	
(lower and upper bound of 95%-confidence interval in brackets) corresponds to Odds Ratio	(2.11 ; 10.04)	Roughly, RRR/PRR/ROR values greater than 2 indicate that this drug-adverse event-combination is 2-fold more likely than all othercombinations.

Table 6. Disproportionality analysis for individual direct acting antiviral agents

Drug	Renalside effects	Other side effects	PRR	ROR
Ombitasvir	2	6	5.53	7.05
Boceprevir	2	7	4.88	5.99
Telaprevir	11	40	4.57	5.55
Paritaprevir	1	6	3.16	3.52
Ritonavir	3	20	2.89	3.17
Dasabuvir	34	247	2.84	3.09
Grazoprevir	4	32	2.46	2.64
Elbasvir	4	32	2.46	2.64
Asunaprevir	36	476	1.58	1.62
Daclatasvir	74	1053	1.52	1.55
Simeprevir	33	553	1.24	1.25
Sofosbuvir	83	1733	1.07	1.07
Atazanavir	0	1	-	-
Ledipasvir	0	1	-	-
Adefovir dipivoxil	0	2	-	-
Velpatasvir	0	1	-	-
Entecavir	0	3	-	-
Tenofovir disoproxil fumarate	0	10	-	-
Odalasvir	0	2	-	-

Performing disproportionate analysis for each DAA separately provided different perspective for renal toxicity Table 6. A PRR and ROR values of more than 2 were observed with ombitasvir, boceprevir, telaprevir, paritaprevir, ritonavir, dasabuvir, grazoprevir, and elbasvir. The limited number of renal toxicity reports observed with ombitasvir (n=2), Boceprevir (n=2), and Paritaprevir (n=1) constraints our ability to draw firm conclusions. Hence, they were not considered statistically associated with incidence of renal side effects.

In order to consider disproportionality results for any of these DAA a pharmacovigilance signal the following conditions must be satisfied: PRR must be greater or equal to two, the chi-squared statistic is greater or equal to 4, and the number of individual cases greater or equal to 3 [24]. Telaprevir and dasabuvir satisfied these conditions. Hence, there is a significant association between the incidence of renal side effects and the administration of telaprevir and dasabuvir. Renal side effects were reported in 34 cases in patients receiving dasabuvir. Similarly, renal side effects were observed in 11 reports from patients that received telaprevir compared to a 40 report of other side effects. This number of cases calls for further investigations using well-designed epidemiologic studies to quantify the risk of developing renal side effects.

Since renal side effect is a broad term, secondary disproportionality analysis was conducted for each renal side effect as side effect of interest. The results are presented in Table 4. Chronic kidney disease, hemodialysis, cystitis Escherichia, and complications of transplanted kidney had a PRR value of more than 2. However, the number of cases was less than two for hemodialysis, cystitis Escherichia, and complications of transplanted kidney. Hence, the incidence of these side effects was not significantly associated with DAA administration. Chronic kidney disease on the other hand was observed in 11 cases with DAA administration. More detailed analysis of chronic kidney disease is presented in Table 5. A chi square of more than 4 (15.5), a PRR of more than 2 (4.59), and a number of cases of more than 2 [11] indicated a significant association between DAA administration and chronic kidney disease.

5. CONCLUSIONS

We reported a significant association between DAA administration and chronic kidney disease and between telaprevir or dasabuvir and renal side effect. These findings are used for hypothesis generation rather than testing. In order to test these findings, it is recommended to conduct non-randomized observational studies or cohort study.

CONSENT

It is not applicable

ETHICS APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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