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Adverse drug reactions during hepatitis C treatment with direct-acting antivirals: The role of medication errors, their impact on treatment discontinuation and their preventability. New insights from the Campania Region (Italy) spontaneous reporting system

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Summary

What is known and Objective: Medication errors, such as unnecessary treatment discontinuation during treatment with direct-acting antivirals (DAAs), can lead to imbalances in the benefit-to-risk ratio. This risk is especially high when the medication error leads to adverse drug reactions (ADRs). However, to date, evidence on the frequency of this phenomenon is scarce. This study aims to provide better insight into ADRs possibly due to medication errors leading to DAA discontinuation and their preventability.

Methods: The Italian Pharmacovigilance Network database was used to extract individual case safety reports (ICSRs) generated from July 2012 to March 2017 via the Campania Region (Italy) spontaneous reporting system. ICSRs that included ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, dasabuvir, daclatasvir, sofosbuvir, simeprevir or elbasvir/grazoprevir as suspected drugs were included in this study. A preventability assessment was then performed utilizing the "P-Method," an algorithm that evaluates known risk factors due to medication errors that can be detected in ICSRs.

Results and discussion: Of the 355 cases included in this study, 6 (1.69%) were classified as preventable and 52 (14.6%) were classified as potentially preventable. The most frequently identified critical criteria (risk factor) for preventable or potentially preventable cases were drug-drug interactions and incorrect drug dosing as part of the antiviral treatment scheme. In total, 89 of the 355 cases (25.1%) discontinued use of the DAAs due to ADRs, of which 20 of the 89 cases (22.5%) were due to an unimportant medical event as classified by the European Medicine Agency important medical event list.

What is new and Conclusion: This study found a proportion of preventable/potentially preventable ADRs involving DAA, which could be improved in the Campania

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Region (Italy). Additionally, the study identified a high proportion of seemingly unnecessary DAA discontinuations among patients who experienced ADRs.

KEYWORDS
adverse reactions, antiviral therapy, direct-acting antivirals, pharmacovigilance

1 | INTRODUCTION

When compared to interferon-based therapies, direct-acting antivirals (DAAs) have radically changed the landscape of the pharmacological treatment of hepatitis C virus (HCV) infections by improving survival, leading to higher sustained virological response (SVR) rates, shorter treatment durations, easier administration and fewer HCV infection-related complications.[1,2] However, real-world data suggest that medication errors, such as unnecessary treatment withdrawal, with this class of drug can lead to an imbalance in the benefit-to-risk ratio.[3-5] A medication error can be defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use."[6] The identification and minimization of medication errors represent a worldwide priority for the optimization of DAA therapies due to their impact on hepatitis C morbidity, prognosis and healthcare burden.[7-9] Accordingly, the World Health Organization promotes activities to detect medication errors that lead to adverse drug reactions (ADRs) by re-evaluating individual case safety reports (ICSRs) submitted through spontaneous reporting systems. Pharmacovigilance Centers are expected to play a key role in this initiative[10-14] by promoting appropriate drug use within their regional territory[15] and by identifying risk factors for ADRs as well as low adherence to pharmacological treatments.[16]

Despite the availability of a validated method for assessing medication errors reported in ICSRs, none of the Italian Pharmacovigilance Regional Centers to date have utilized these data in studies to evaluate the impact of medication errors involving DAAs. This study aimed to fulfil this new regulatory task while providing further insight into this topic by assessing ADRs involving DAAs, ADRs leading to DAA discontinuation and preventing these events by evaluating all ICSRs sent through Campania spontaneous reporting system that reported these drugs as suspected.

IMPACTS OF FINDINGS ON PRACTICE STATEMENTS

- Clinicians should always check for potential drug-drug interactions when drugs are coadministered with DAAs.
- Clinicians should always check for unstable or uncontrolled cardiac disease when ribavirin is coadministered with DAAs.
- DAAs should not be discontinued due to unimportant medical events, and clinicians should advocate for persistent treatment with DAAs.
- Ribavirin should not be underdosed if ribavirin-induced anaemia occurs.

2 | METHODS

2.1 | Data collection

The Italian Pharmacovigilance Network database was screened to extract ICSRs reported from July 2012 to March 2017 through the Campania Region spontaneous reporting system. ICSRs listing ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, dasabuvir, daclatasvir, sofosbuvir, simeprevir or elbasvir/grazoprevir as a suspected drug were selected.

2.2 | Preventability assessment

The P-method is a validated algorithm developed to assess the preventability of ADRs using records sent through the spontaneous reporting system; this method is applied by a trained multidisciplinary team composed of clinical pharmacologists with pluriannual experience in Pharmacovigilance as described previously.[10-13] Cases were classified as potentially preventable if there was at least one critical criterion for preventability in the ICSR. However, due to a lack of detail on the method's administration procedures, laboratory monitoring or the use of a pharmacological therapy, identifying associations between the preventability criterion and adverse drug reactions was not possible. The "Summary of Product Characteristics" (SmPC) published by the Italian Medicine Agency was used for all evaluations that required information provided by the SmPC, and ICSRs were classified as "documented" or "non-documented" in accordance with the procedure described by Benkirane et al[13]

2.3 | Adverse drug reactions leading to direct-acting antivirals discontinuation

Adverse drug reactions associated with discontinuation of direct-acting antiviral agents were tabulated. The causes of discontinuation were classified as either an "important" or a "not important" medical event, in accordance with the important medical event

list developed by the European Medicine Agency (IME list, version 20.0).[17] Boxplots representing the time to discontinuation were generated for each direct-acting antiviral agent. Time to discontinuation was calculated by measuring the difference in days between the start date of an antiviral treatment and the date of discontinuation.

2.4 | Descriptive analyses

Information on the year of the report, age, sex, seriousness, outcome, reporters, actions taken to solve the adverse event, causality assessment and concomitant medical products was provided separately for the "preventable" and "not preventable" ICSRs. Additionally, these data were provided separately for the ICSRs that reported a discontinuation of the antiviral treatment and those that did not. For aforementioned purposes, seriousness was codified as it is described in the International Council on Harmonization E2D guidelines.[18] To measure outcome, and in accordance with Italian ICSR reporting form, six categories were used: recovered, improvement, resolution with sequelae, unchanged clinical condition, death and not available. The causality assessment evaluation was performed via the Naranjo algorithm.[19]

3 | RESULTS

Approximately 34 000 patients were infected with hepatitis C in the Campania Region during 2017. By March of 2017, a total of 5409 patients were treated with ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, dasabuvir, daclatasvir, sofosbuvir, simeprevir or elbasvir/grazoprevir for HCV infections.[20] In the period of July 2012 to March 2017, 355 of 21,424 ICSRs sent to Campania Pharmacovigilance Regional Centre listed ledipasvir/sofosbuvir, dasabuvir, daclatasvir, sofosbuvir, simeprevir ombitasvir/paritaprevir/ritonavir or elbasvir/grazoprevir as suspected drugs. The reporting rate was seven ICSRs per 100 patients (more than one ADR could be reported in each ICSR and more than one ICSR could be reported for the same patient). Anaemia (94/616; 15.2%) and asthenia (42/616; 6.8%) were the most commonly reported ADRs (Table S1 in Appendix S1), and hospital physicians were the most common reporter, sending 280 (78.5%) of 355 ICSRs. The causality assessment determined that causality was possible for 348 cases (98.0%), probable for six cases (1.7%) and doubtful for one case (0.3%). Therefore, the preventability assessment was performed for 354 cases (99.7%).

3.1 | Preventable cases

By reassessing each ICSR according to the critical criteria of the P-method, six cases (1.69%) of 355 were identified as preventable, and full agreement was reached for all cases by the multidisciplinary team involved in the preventability assessment. In all preventable cases, the underlying mechanism of the ADR was dose-related (Figure 1). Six critical criteria were detected, of which five of six (83.3%) related to the practices of healthcare professionals and one of six (16.7%) related to patient behaviour. All adverse drug reactions reported in preventable cases were serious and associated with a negative prognosis (Table 1). In five of six cases (83.3%), pharmacological and/or nonpharmacological treatments, drug switch or withdrawal was required. Clinical and socio-demographic characteristics of both the preventable and not preventable cases are shown in Table 1.

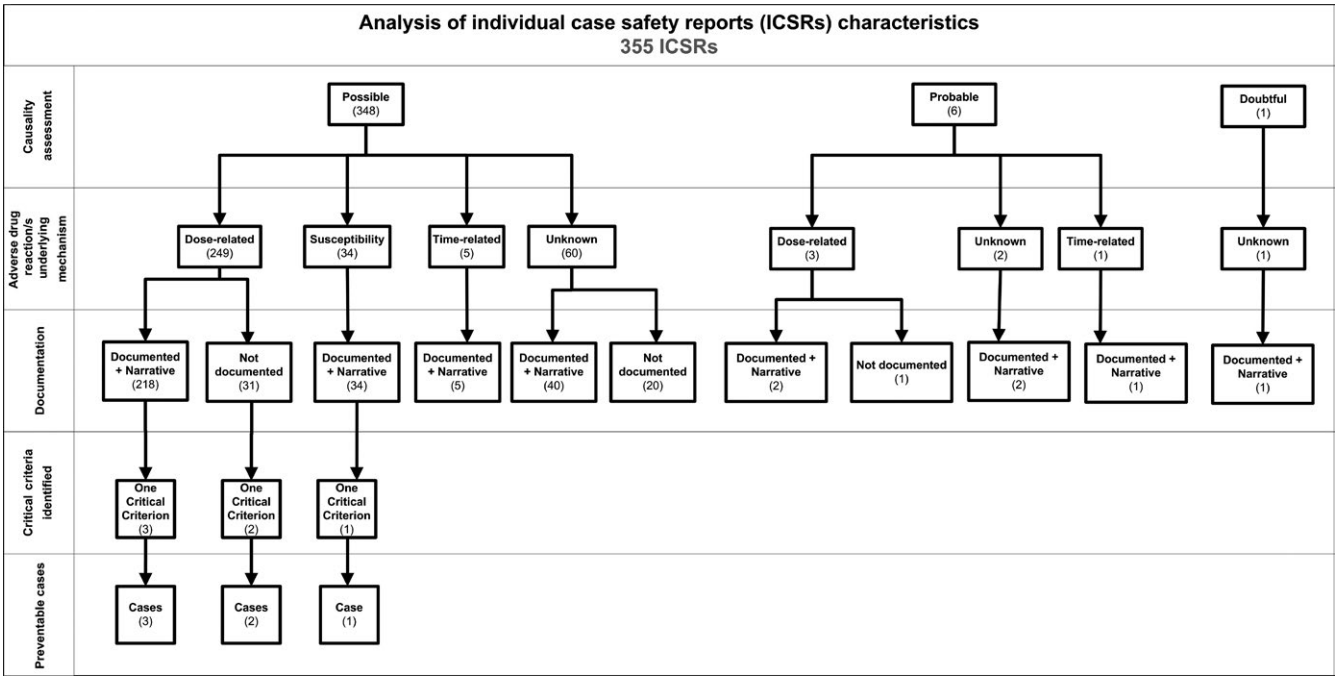


Figure 1. Characteristics of individual case safety reports involving ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, dasabuvir, daclatasvir, sofosbuvir, simeprevir or elbasvir/grazoprevir recognized in the Campania spontaneous reporting system from July 2012 to March 2017

3.1.1 | Preventable cases with critical criteria related to healthcare professionals' practices

The most commonly detected critical criterion related to the practices of healthcare professionals was drug-drug interaction (3/5; 60.0%). In the first case, simeprevir was administered concurrently with verapamil leading to dermatitis.[21] In the second case, a drug-drug interaction between ledipasvir/sofosbuvir and digoxin led to bradycardia and vomiting.[22] In the third case, the coadministration of ledipasvir/sofosbuvir and ranitidine led to an increase in the viral load of hepatitis C. The critical criteria in the remaining two cases were inappropriate prescription according to the patients' characteristics and incorrect dosage. In particular, a case with a medical history of heart failure, hypertension, venous insufficiency and chronic obstructive pulmonary disease was treated with ribavirin that led to a further deterioration of their heart failure symptoms. In the other case, ombitasvir/paritaprevir/ritonavir, dasabuvir and ribavirin were underdosed as defined in the summary of these medication's product characteristics,[23,24] leading to ascites, liver cirrhosis and hepatic encephalopathy.

Table 1. Demographic and clinical characteristics of preventable and not preventable cases involving suspected treatment with ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, dasabuvir, daclatasvir, sofosbuvir, simeprevir or elbasvir/grazoprevir. ICSRs were screened among those reported to the Campania spontaneous reporting system from July 2012 to March 2017

Variable	Level	Not preventable (n = 349)	Preventable (n = 6)	Total (n = 355)
Year	2014	16 (4.6)	0 (0.0)	16 (4.5)
	2015	147 (42.1)	3 (50.0)	150 (42.3)
	2016	163 (46.7)	3 (50.0)	166 (46.8)
	2017	23 (6.6)	0 (0.0)	23 (6.5)
Age	Mean (SD)	65.5 (10.2)	69.8 (2.5)	65.6 (10.1)
Sex	Female	162 (46.8)	4 (66.7)	166 (47.2)
	Male	184 (53.2)	2 (33.3)	186 (52.8)
	Missing	3	0	3
Seriousness	Death	12 (3.4)	1 (16.7)	13 (3.7)
	Not defined	5 (1.4)	0 (0.0)	5 (1.4)
	Not serious	158 (45.3)	0 (0.0)	158 (44.5)
	Serious—hospitalization	53 (15.2)	1 (16.7)	54 (15.2)
	Serious—life threatening	5 (1.4)	0 (0.0)	5 (1.4)
	Serious—other clinically significant condition	116 (33.2)	4 (66.7)	120 (33.8)
Outcome	Death	17 (4.9)	1 (16.7)	18 (5.1)
	Improvement	86 (24.6)	0 (0.0)	86 (24.2)
	Not available	79 (22.6)	1 (16.7)	80 (22.5)
	Recovered	56 (16.0)	1 (16.7)	57 (16.1)
	Resolution with sequelae	7 (2.0)	0 (0.0)	7 (2.0)
	Unchanged clinical condition	104 (29.8)	3 (50.0)	107 (30.1)
Reporter	General practitioner	1 (0.3)	0 (0.0)	1 (0.3)
	Hospital physician	274 (78.5)	6 (100.0)	280 (78.9)
	Not defined	7 (2.0)	0 (0.0)	7 (2.0)
	Nurse	1 (0.3)	0 (0.0)	1 (0.3)
	Other healthcare professions	14 (4.0)	0 (0.0)	14 (3.9)
	Pharmacist	2 (0.6)	0 (0.0)	2 (0.6)
	Specialist	50 (14.3)	0 (0.0)	50 (14.1)
Action taken	No	85 (24.4)	1 (16.7)	86 (24.2)
	Yes	264 (75.6)	5 (83.3)	269 (75.8)
Causality	Doubtful	1 (0.3)	0 (0.0)	1 (0.3)
	Possible	342 (98.0)	6 (100.0)	348 (98.0)
	Probable	6 (1.7)	0 (0.0)	6 (1.7)
Medical products	>1	228 (65.3)	4 (66.7)	232 (65.4)
	1	121 (34.7)	2 (33.3)	123 (34.6)

3.1.2 | Preventable cases with critical criteria related to patient behaviour

In one case, the patient arbitrarily used nontherapeutic (higher) oral doses of ombitasvir, paritaprevir, ritonavir and dasabuvir for 8 days leading to the development of anaemia.

3.1.3 | Potentially preventable cases

In total, 52 of 355 cases (14.6%) were classified as potentially preventable, and the primary critical criterion identified was an incorrect dose (Table 2). In cases in which an incorrect dose was identified, ribavirin was the drug most commonly associated with DAAs. In particular, ribavirin was underdosed based on the expected posology when coadministered with DAAs. Details of the potentially preventable cases are provided in Table 2.

3.2 | Adverse drug reactions leading to discontinuation of direct-acting antivirals

Eighty-nine of 355 cases (25.1%) discontinued the use of DAAs due to ADRs, of which 20 of 89 cases (22.5%) were due to a "not important" medical event (Figure 2). The clinical and demographic characteristics of cases that discontinued vs those that persisted with DAA treatment are provided in Table S2 of online Appendix S1. The median time for days until discontinuation was 77, 27, 23, 28, 33 and 48 for daclatasvir, dasabuvir, ombitasvir/paritaprevir/ritonavir, simeprevir, sofosbuvir and sofosbuvir/ledipasvir, respectively (Figure 2), suggesting that the majority of discontinuation occurred within the first month of treatment. The top three most reported not important medical events associated with drug discontinuation were depression, panic attacks and arthralgia. All ADRs associated with drug discontinuation are shown in Table 3.

4 | DISCUSSION

This study is part of a set of initiatives to promote drug safety developed by the Campania Pharmacovigilance Regional Centre during the last decade.[11,25-29] By re-evaluating the ICSRs, we found that <2% of cases were deemed preventable. The most commonly detected preventable criterion was labelled drug-drug interaction of coadministered drugs with DAA. This finding is in-line with previous results from other sources that emphasized the critical role of drug-drug interactions with the pharmacological use of this drug class.[1,30-32] Direct antiviral agents are a substrate of CYP3A, CYP2C9, CYP2C19 or P-glycoprotein, key proteins, involved in the metabolism and/or transport of several drugs.[33] As a result, they can function as both victims and culprits in drug-drug interactions by acting as enzyme inhibitors or inducers or by altering drug transportation mediated by P-glycoprotein. This interaction was demonstrated in our study by the association of ledipasvir, in combination with digoxin, with the symptomatic development of digoxin intoxication including bradycardia and vomiting. This effect is a consequence of ledipasvir inhibiting the P-glycoprotein-mediated intestinal efflux of digoxin, which leads to an increase in digoxin serum levels and its related pharmacologic effects.[22] Similarly, simeprevir, in combination with verapamil, was found to be associated with the development of verapamil-induced dermatitis. According to simeprevir's SmPC, concurrent use of simeprevir and verapamil can lead to increased plasma concentrations and pharmacologic effects of verapamil. The mechanism involves simeprevir-induced inhibition of CYP450 3A4-mediated metabolism and P-glycoprotein-mediated efflux of verapamil in the intestine.[34] In another case, ledipasvir was coprescribed with ranitidine resulting in an increase in hepatitis C viral load. Coadministration of ledipasvir with H2-receptor antagonists can lead to reduced ledipasvir gastrointestinal absorption due to ledipasvir's pH-dependent solubility with higher solubility at lower pH values. Additionally, we identified a case with a medical history of severe heart failure that was treated with ribavirin in combination with DAA. According to ribavirin's SmPC, it is contraindicated for patients with a recent medical history of unstable or uncontrolled cardiac disease.[24] In this case, the ADR experienced by the patient was further deterioration of their heart failure symptoms.

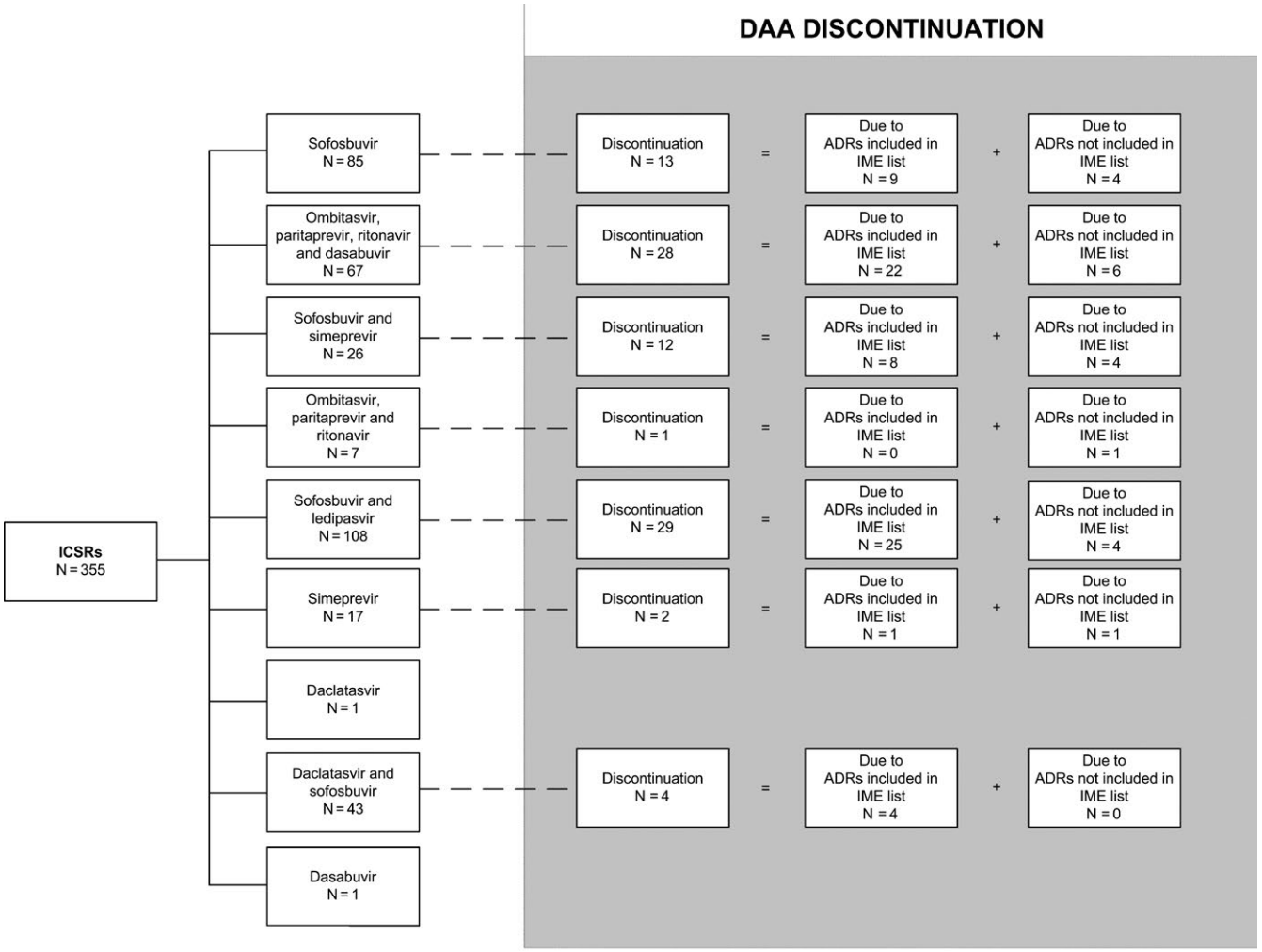
We also identified preventable or potentially preventable cases in which DAA or ribavirin was underdosed, resulting in therapeutic failure. In the majority of cases, ribavirin, a drug coadministered with DAA that is crucial for the success of the antiviral treatment, was underdosed based on patient's body weight. Based on the data collected during our active pharmacovigilance monitoring of the clinicians who prescribed the DAA, it was determined that the main factor driving the choice to underdose ribavirin was the fear of causing ribavirin-induced severe anaemia. Randomized clinical trials showed that patients who developed anaemia due to ribavirin experienced a greater benefit from erythropoietin-alfa administration than that from ribavirin dose reduction. In fact, administration of erythropoietin-alfa was able to reduce the requirement for a ribavirin dose reduction, leading to a higher sustained virological response and an improvement to the patients' quality of life.[35,36] Moreover, in patients with hepatitis C who experienced ribavirin-induced anaemia, the loss in haemoglobin was found to be a more reliable pharmacodynamic biomarker of ribavirin's antiviral efficacy than its ingested dosage.[37] Based on these results, there is a clear necessity to disseminate the collective experiences and knowledge of the preventability criteria for these drugs to healthcare operators involved in the pharmacological treatment with direct-acting antivirals. To achieve this goal, clinical pharmacologists from the Pharmacovigilance Center will support clinicians in the prescription process by promoting the appropriate use of these drugs.

Finally, one of the most important findings of this study was the high proportion of DAA discontinuation in cases that experienced an ADR (25.1%). Most of these discontinuations occurred within the first month of treatment, and a high proportion of the associated ADRs were classified as not important medical events, as defined by the European Medicine Agency, highlighting a critical aspect of DAA treatment. Improvements in DAAs resulted in

Table 2. Potentially preventable cases involving suspected treatment with ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, dasabuvir, daclatasvir, sofosbuvir, simeprevir or elbasvir/grazoprevir. ICSRs were screened among those reported to the Campania spontaneous reporting system from July 2012 to March 2017

Active ingredients	Preventability criterion/criteria	Missing information	What was the missing information important for	Most reported adverse drug reactions	Number of cases
Ribavirin	Incorrect dose	Comorbidities	Cases with a nontherapeutic dosage of ribavirin (lower). According to ribavirin SmPC, dosing of ribavirin is determined by the patient body weight and comorbidities	Therapeutic failure, HCV viral load increase, ascites, hepatic injury or jaundice	5
	Incorrect laboratory monitoring	Laboratory examinations	According to ribavirin SmPC, laboratory evaluations of bilirubin are to be conducted at weeks 2 and 4 of antiviral therapy and periodically thereafter as clinically appropriate.	Jaundice	1
Dasabuvir, ombitasvir, paritaprevir and ritonavir	Wrong indication/incorrect prescription according to the patient medical condition	HCV genotype	In three cases, the indication of use of aforementioned drugs was imprecise. In particular, no information was reported regarding HCV genotypes. According to dasabuvir, ombitasvir, paritaprevir and ritonavir SmPCs, these active ingredients are indicated for specific HCV genotypes (HCV genotype 1a/b, 4)	Increased blood bilirubin, lack of efficacy, jaundice and ascites	22
Ledipasvir and sofosbuvir	Wrong indication/incorrect prescription according to the patient medical condition	HCV genotype	In three cases, the indication of use of aforementioned drugs was imprecise. In particular, no information was reported regarding HCV genotypes. According to ledipasvir and sofosbuvir SmPCs, these active ingredients are indicated for specific HCV genotypes (HCV genotype 1, 3, 4, 5 or 6)	Increased blood bilirubin, lack of efficacy and ascites	18
	Labelled drug-drug interaction: omeprazole and ledipasvir/sofosbuvir	Administration protocol	According to ledipasvir/sofosbuvir SmPCs, proton pump inhibitors should not be taken before ledipasvir/sofosbuvir. In this case, it is not known whether the proton pump inhibitors were taken before or after ledipasvir/sofosbuvir	Dysphagia and dyspepsia	1
Daclatasvir	Wrong indication/incorrect prescription according to the patient medical condition	HCV genotype	In three cases, the indication of use of aforementioned drugs was imprecise. In particular, no information was reported regarding HCV genotypes. According to ledipasvir and sofosbuvir SmPCs, these active ingredients are indicated for specific HCV genotypes (HCV genotype 1, 3, 4, 5 or 6)	Lack of efficacy and jaundice	5

HCV, hepatitis C virus; SmPC, Summary of Product Characteristics.



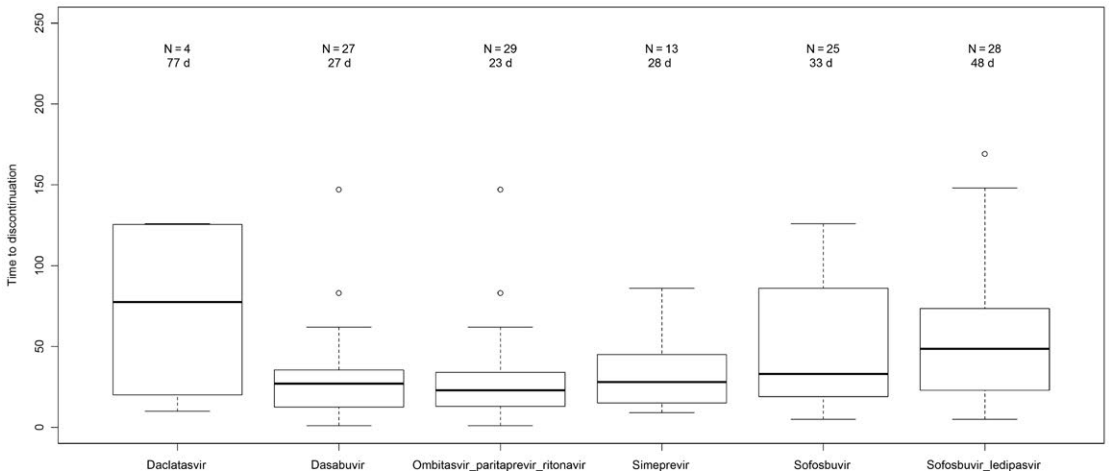


Figure 2. Adverse drug reactions leading to ledipasvir/sofosbuvir, dasabuvir, daclatasvir, sofosbuvir, simeprevir, ombitasvir/paritaprevir/ritonavir or elbasvir/grazoprevir discontinuation. ICSRs were screened among those reported to the Campania spontaneous reporting system from July 2012 to March 2017. *In four cases, there was no information on the start date or end date of antiviral treatment. DAA, direct-acting antivirals; ADR, adverse drug reactions; IME, important medical event; ICSRs, individual case safety reports

better safety profiles and a simplified administration schedule to promote a higher adherence to the pharmacological treatment of patients with hepatitis C,[38,39] but despite these improvements, ADRs still represent a key element for poor adherence to this pharmacological treatment. This issue is a crucial component as nonadherent patients who discontinue treatment due to ADRs have a statistically lower sustained virological response (SVR) compared to that of adherent patients who experience the same

Table 3. Adverse drug reactions leading to ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, dasabuvir, daclatasvir, sofosbuvir, simeprevir or elbasvir/grazoprevir discontinuation. ICSRs were screened among those reported to the Campania spontaneous reporting system from July 2012 to March 2017

Distribution of discontinuation causes by direct-acting antiviral agents	In IME list	Not in IME list	Total
Daclatasvir and sofosbuvir	4		4
Aphasia	1		1
Heart failure (worsening)	1		1
Hypersensitivity	1		1
Retinal haemorrhage	1		1
Ombitasvir, paritaprevir and ritonavir		1	1
Hypotension		1	1
Ombitasvir, paritaprevir, ritonavir and dasabuvir	22	6	28
Anaemia	2		2
Arthritis		2	2
Ascites	5		5
Asthenia		1	1
Atrioventricular block	1		1
Bacterial peritonitis	1		1
Disorientation		1	1
Heart failure	3		3
Hepatic encephalopathy	1		1
Hypersensitivity	3		3
Hypertensive crisis	1		1
Jaundice	5		5
Lack of efficacy		1	1
Panic attack		1	1
Simeprevir	1	1	2
Jaundice	1		1
Photosensitization dermatitis		1	1
Sofosbuvir	9	4	13
Anaemia	2		2
Arrhythmia	1		1
Bowel infarction	1		1
Burning sensation		1	1
Depression		2	2
Haemorrhagic anaemia	1		1
Hyperglycaemia		1	1
Pancreatitis	1		1
Portal vein thrombosis	1		1
Reduced creatinine clearance	1		1
Tachycardia	1		1
Sofosbuvir and ledipasvir	25	4	29
Anaemia	3		3
Arthralgia		1	1
Ascites	3		3
Bradycardia	1		1
Brain haemorrhage	1		1
Depression		1	1
Disseminated intravascular coagulation	1		1
Gastrointestinal perforation	1		1
Haemoperitoneum	1		1
Heart failure (worsening)	1		1
Haematemesis	1		1
Hepatic encephalopathy	2		2
Hepatic tumour	1		1
Hyperbilirubinemia	1		1
Hypersensitivity	3		3
Mood disorder		1	1
Myocardial infarction	2		2
Panic attack		1	1
Rupture of oesophageal varices	1		1
Stroke	2		2
Sofosbuvir and simeprevir	8	4	12
Angina	1		1
Asthenia		1	1
Bacterial peritonitis	1		1
Confusion		1	1
Heart failure	1		1
Haematemesis	1		1
Hepatic encephalopathy	2		2
Hypersensitivity	1		1
Increased transaminase		1	1
Lack of efficacy		1	1
Portal vein thrombosis	1		1

IME term list, important medical event terms list.
Accessible at http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500208836.

adverse event.[40] Our results are in-line with those of Younossi et al, [40] which suggest that a high proportion of patients with chronic hepatitis C who had poor adherence to DAA treatment experienced fatigue, flu-like symptoms, psychiatric disorders (such as depression and panic attacks) and musculoskeletal disorders (such as arthralgia). In these regards, it should be highlighted that paroxetine and citalopram have been successfully used for treatments of both hepatitis C-related depression and for the prevention and treatment of interferon-related depression. Considering the pathophysiological mechanism of HCV/interferon-induced depression, the use of the aforementioned drugs could be considered rational. In fact, previous studies proved that interferon could promote a reduction in synaptic concentrations of serotonin.[41]

Additionally, HCV is not a formal contraindication for paroxetine and citalopram usage (according to their SmPC). We therefore believe that it is crucial in our regional territory to promote practitioner's oversight and motivation of patients treated with these drugs to try to better manage ADRs instead of suspending the pharmacological treatment. In addition, real-world data suggest that the application of pharmacogenetic tests to understand and prevent drug-related complications could help clinicians identify patients with an increased risk of experiencing ADRs. As a result, the emerging field of "pharmacogenovigilance" seeks to address these unanswered questions by combining the expertise of both pharmacovigilance and pharmacogenetics.[42,43]

5 | STRENGTHS AND LIMITATIONS

The use of the "P-Method" is an important strength of this study because it is a validated tool provided by the WHO to assess the preventability of adverse drug reactions. Conversely, one major limitation of this study is that we cannot rule out selection bias as our study sample represents only a small proportion of a region in Italy, and our results may not be generalizable to other settings. This study also has the intrinsic limitations of the spontaneous reporting method, which have been described previously,[44] and it should be noted that 98% of the reports were deemed only "possible" using the Naranjo causality assessment.

6 | CONCLUSIONS

This study found a proportion of preventable ADRs involving DAA, which could be a target for improvement. Additionally, a high proportion of DAA discontinuations were found among patients who experienced ADRs. These findings should serve as a call to action for physicians to promote the appropriate use of these drugs and to improve patient adherence, particularly among those who experience ADRs during treatment with DAAs.

COMPLIANCE WITH ETHICAL STANDARDS

No ethical approval was necessary due to the exclusive use of anonymous patient data.

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CONFLICT OF INTEREST

Nothing to disclose.

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