Comorbidities and concomitant medications in patients with chronic hepatitis C virus infection receiving second-generation direct-acting antiviral regimens in Belgium : an observational study

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Abstract

***Objective* : To describe comorbidities and concomitant medications in patients initiating treatment for hepatitis C virus (HCV) infection with direct-acting antiviral (DAA) regimens in Belgium.**

***Methods* : This was a noninterventional, observational, multi-center study of data from patient charts. Adult patients with HCV infection receiving second-generation DAA therapy were included. Comorbidities were assessed at the time of HCV treatment initiation. Concomitant medications were recorded at the time of diagnosis and at treatment initiation. Potential clinically relevant drug-drug interactions (DDIs) were assessed based on information available at www.hep-druginteractions.org. The primary objective was to describe concomitant medication use ; secondary objectives were to describe modifications in concomitant therapies and comorbidities.**

***Results* : 405 patients were included. A total of 956 comorbidities were reported by 362 patients (median, 2 ; range, 0-15). The most common comorbidities were hypertension (27.2%) ; HIV coinfection (22.5%), and type 2 diabetes mellitus (14.3%). Overall, 1455 concomitant medications were being taken by 365 patients (90.1% ; median, 3 ; range 0-16). The most common concomitant medications were psycholeptics (28.6%), antiviral agents (24.2%), and medications for acid-related disorders (21.0%) Overall, 74/365 (20.3%) patients receiving a concomitant medication required an adaptation to their concomitant medication. The medications that most frequently required change were drugs for acid-related disorders (n = 14) and antiviral drugs (n = 5) ; those that were most frequently stopped were lipid-modifying drugs (n = 25) and drugs for acid-related disorders (n = 13).**

***Conclusion* : Physicians are aware of the potential for DDIs with DAAs, but improved alignment between clinical practice and theoretical recommendations is required.** (Acta gastroenterol. belg., **2021**, 84, **33-41**).

Keywords : hepatitis C, drug–drug interactions, direct-acting antivirals, Belgium, co-medication.

Introduction

The introduction of direct-acting antiviral agents (DAAs) has revolutionized the treatment of chronic hepatitis C virus (HCV) infection. Modern HCV treatment regimens are generally simple, once-daily, short-duration regimens that are well-tolerated and achieve cure rates in excess of 90% (1, 2). Second-generation pangenotypic regimens are now available that are suitable for the majority of people with chronic HCV infection. The combinations of sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir are approved for treatment of treatment-naive and treatment-experienced individuals with or without compensated cirrhosis, regardless of HCV genotype, whereas other regimens, including elbasvir/grazoprevir (EBR/GZR), ombitasvir/paritaprevir/ritonavir ± dasabuvir (OBV/PTVr ± DSV), and sofosbuvir/ledipasvir (SOF/LED) are recommended for specific HCV genotypes (1).

The estimated prevalence of HCV viremia in Belgium is 0.12%, amounting to 13 320 chronically infected individuals (3, 4). Access to DAAs for HCV infection is a critical factor in the stride towards the 2030 World Health Organization elimination targets. In Belgium, reimbursement of HCV therapies is open to all individuals with HCV infection (5), but prior to January 2019, reimbursement was limited to those with liver fibrosis stage ≥F2 and to those in certain high-risk groups, such as those with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) coinfection ; those listed for or recipients of solid organ, hematopoietic stem cell, or bone marrow transplant ; those with severe extrahepatic illness ; those on dialysis ; and those with hemoglobinopathy, hemophilia, or other coagulation disorders (6, 7).

Current European guidelines for the treatment of HCV infection note that numerous and complex drug–drug interactions (DDI) are possible with HCV DAA regimens (1). Particular consideration is required when treating HIV-coinfected individuals, with several HIV antiviral drugs either contraindicated or requiring dose modifications when used alongside HCV treatment regimens. DDIs are also known to exist between HCV

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treatment regimens and lipid-lowering agents, central nervous system drugs, and medications for acid-related disorders (1). In general terms, nonstructural protein 3/4A (NS3/4A) protease inhibitors, and nonstructural protein 5A (NS5A) inhibitors have had clinically significant interactions with concomitant medication metabolized by the cytochrome P450 (CYP) 3A4, P-glycoprotein, organic anion transporting polypeptide transporters, or breast cancer resistance protein. The nucleotide polymerase inhibitor sofosbuvir is also a p-glycoprotein substrate (8). Thus, a thorough risk assessment is required for all people with HCV infection prior to starting DAA treatment and prior to initiating other medications while receiving DAAs. The aim of this study was to describe comorbidities and the use and dose modification of concomitant medications in individuals initiating treatment for HCV infection with DAA regimens in Belgium.

Methods

This was a noninterventional, observational, multicenter study conducted at 11 study sites in Belgium. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Independent institutional review boards or ethics committees reviewed and approved the protocol and applicable amendments for each institution, and central Ethics Committee (Antwerp University Hospital ; Belgisch Registratienummer : B300201630554) approval was received on December 19, 2016. All participants gave written informed consent.

Patients

Adult male and female patients (aged ≥18 years) with HCV infection receiving second-generation DAA therapy were included. Patients were either treatment-naive or treatment-experienced and were enrolled regardless of comorbidities or concomitant medications. Patients with F0-F4 fibrosis were eligible for inclusion in the study ; however, those with F0-F1 fibrosis were required to be eligible for treatment reimbursement in Belgium (defined as high-risk patients), and those with F4 cirrhosis were required to have Child-Pugh A disease stage.

Patients aged <18 years, those with F0–F1 fibrosis who were not eligible for reimbursement, and cirrhotic patients with Child-Pugh B or C disease were excluded.

Study design

This was a noninterventional study based on secondary use of data collected from patient charts. The administration of therapeutic or prophylactic agents was not required in the protocol, and there were no procedures required as part of the protocol. Data collection was divided into prospective and retrospective parts. Eligibility for inclusion in each part of the study reflects Belgium reimbursement criteria at the time that the study was performed. In the prospective part of the study, data were collected from patients starting DAA treatment for HCV infection between January 9, 2017, and October 31, 2017. To be eligible for inclusion in this part of the study, patients were required to have F0-F2 fibrosis and be initiating treatment with EBR/GZR, SOF/LED, OBV/PTVr/ ± DSV, SOF + daclatasvir (DAC), or SOF/VEL ; or to have F3–F4 fibrosis and be initiating treatment with EBR/GZR or SOF/VEL. The retrospective part of the study included patients with F3–F4 fibrosis who started treatment with SOF/LED, OBV/PTVr ± DSV, or SOF + DAC before January 1, 2017.

Comorbidities were assessed at the time of HCV treatment initiation. Concomitant medications were recorded at the time of diagnosis (prior to any adjustment in concomitant medication regimen) and again at the time of treatment initiation (after any adjustment to concomitant medication was complete), permitting an assessment of the adjustments made prior to HCV treatment initiation. Potential clinically relevant DDIs (coadministration of drugs that may require dose adjustment/closer monitoring) were assessed in August 2018 based on information available at www.hep-druginteractions.org.

Objectives

The primary objective of this study was to describe concomitant medication use in patients with HCV infection receiving DAA therapy in Belgium, who were analyzed according to fibrosis stage, presence or absence of cirrhosis, and DAA treatment regimen. The secondary objectives were to describe modifications in concomitant therapies according to HCV treatment regimen and to describe comorbidities in these patients.

Statistics

All data were analyzed descriptively, and no inferential statistics were applied. For categorical variables, numbers and percentages of patients are reported, and for continuous variables, the mean, standard deviation (SD), or median (range) were determined together with the total number of observations and the number of missing values. Missing values were not imputed but were analyzed as a separate category. Demographics and other baseline characteristics are presented by treatment, and concomitant medications and comorbidities were coded using the WHO drug dictionary and the Medical Dictionary for Regulatory Activities (MedDRA), respectively (9). Fisher's exact test was used for testing overall comparisons ($P \leq 0.05$ was considered significant) and for comparison between different treatment groups (10 pairwise tests). A Bonferroni correction was performed to correct for multiple testing ($P \leq 0.005$ was considered significant).

Results

Patient characteristics

A total of 419 patients were enrolled in the present analysis, with clinic visit dates between January 9, 2017, and October 31, 2017. DAA treatment for HCV infection in the retrospective part of the study was started between August 3, 2015, and December 19, 2016 ; and HCV treatment in the prospective part of the study was started between January 11, 2017, and November 22, 2017. Data were collected retrospectively from 89 patients (22.0%) and prospectively from 316 patients (78.0%). Fourteen patients were excluded because of violation in their allocation to the retrospective/prospective data collection (7 patients with F3 fibrosis and 2 with F4 fibrosis started SOF + DAC in 2017 ; 3 patients with F3 fibrosis and 1 with F4 fibrosis started OBV/PTV/r ± DSV in 2017 ;

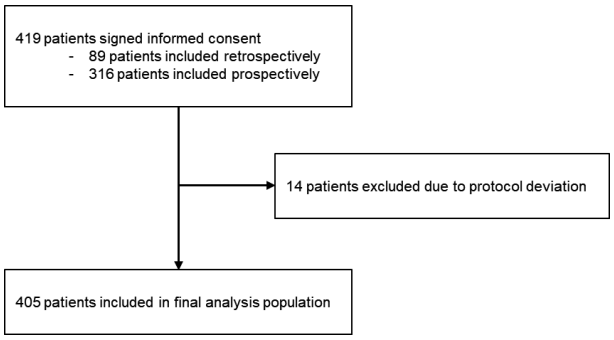

Figure 1. — Flowchart of patients included in study and final analysis population.

Table 1. — **Patient characteristics**

	EBR/GZR ± RBV	OBV/PTVr ± DSV± RBV	SOF + DAC ± RBV	LED/SOF ± RBV	SOF/VEL ± RBV	All Patients
	N=111	*N*=34	*N* = 107	*N*=27	*N*=126	*N*=405
Data acquisition, *n* (%)						
Prospective	111 (100)	13 (38.2)	57 (53.3)	9 (33.3)	126 (100)	316 (78.0)
Retrospective	0 (0)	21 (61.8)	50 (46.7)	18 (66.7)	0 (0)	89 (22.0)
Sex, *n* (%)						
Male	55 (49.5)	14 (41.2)	76 (71.0)	14 (51.9)	86 (68.3)	245 (60.6)
Female	56 (50.5)	20 (58.8)	31 (29.0)	13 (48.1)	40 (31.7)	160 (39.5)
Age						
Mean (SD)	58.23 (14.3)	61.50 (15.9)	51.03 (11.6)	61.30 (12.1)	55.06 (12.2)	55.82 (13.4)
Median (range)	56.0 (29.0-90.0)	63.5 (24.0-88.0)	52.0 (25.0-80.0)	62.0 (42.0-84.0)	54.0 (27.0-85.0)	55.0 (24.0-90.0)
<65 years	74 (66.7)	18 (52.9)	95 (88.8)	15 (55.6)	99 (78.6)	301 (74.3)
≥65 years	37 (33.3)	16 (47.1)	12 (11.2)	12 (44.4)	27 (21.4)	104 (25.7)
HCV treatment history, *n* (%)						
Naive	84 (76.7)	21 (61.8)	72 (67.3)	17 (63.0)	84 (66.7)	278 (68.6)
Experienced	27 (24.3)	27 (24.3)	35 (32.7)	10 (37.0)	42 (33.3)	127 (31.4)
HCV genotype, *n* (%)						
GT1a	26 (23.6)	3 (8.8)	39 (36.4)	3 (11.1)	41 (32.5)	112 (27.7)
GT1b	51 (46.4)	26 (76.5)	16 (15.0)	11 (40.7)	16 (12.7)	120 (29.7)
GT1-other	2 (1.8)	0 (0)	0 (0)	1 (3.7)	4 (3.2)	7 (1.6)
GT2	0 (0)	0 (0)	3 (2.8)	0 (0)	11 (8.7)	14 (3.5)
GT3	0 (0)	0 (0)	33 (30.8)	0 (0)	28 (22.2)	61 (15.1)
4	31 (28.2)	5 (14.7)	15 (14.0)	12 (44.4)	17 (13.5)	80 (19.8)
5	0 (0)	0 (0)	1 (0.9)	0 (0)	7 (5.6)	8 (2.0)
6	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.6)	2 (0.5)
Fibrosis stage, *n* (%)						
F0–F1	21 (18.9)	2 (5.9)	8 (7.5)	6 (22.2)	22 (17.5)	59 (14.6)
F2	51 (45.9)	11 (32.4)	49 (45.8)	3 (11.1)	53 (42.1)	167 (41.2)
F3	26 (23.4)		23 (21.5)[b]	6 (22.2)[b]	32 (25.4)	96 (23.7)
F4[a]	13 (11.7)		27 (25.2)[b]	12 (44.4)[b]	19 (15.1)	83 (20.5)
HIV coinfection status, *n* (%)						
No	(85.6)	(91.2)	74 (69.2)	(59.3)	(77.8)	314 (77.5)
Yes	(14.4)	(8.8)	33 (30.8)	(40.7)	(22.2)	91 (22.5)
Receiving ribavirin, *n* (%)						
Yes	(7.2)	(35.3)	74 (69.2)	(37.0)		116 (28.6)
No	103 (92.8)	22 (64.7)	33 (30.8)	17 (63.0)	114 (90.5)	289(71.4)

DAC, daclatasvir ; DSV, dasabuvir ; EBR, elbasvir ; GT, genotype ; GZR, grazoprevir ; HCV, hepatitis C virus ; HIV, human immunodeficiency virus ; LED, ledipasvir ; OBV, ombitasvir ; PTVr, paritaprevir/ritonavir ; RBV, ribavirin ; SD, standard deviation ; SOF, sofosbuvir. [a]Child-Pugh A cirrhosis. [b]Data from patients with F3–F4 fibrosis receiving OBV/PTVr ± DSV, SOF+DAC, or LED/SOF were collected retrospectively (n = 89). Data from all remaining patients were collected prospectively (n = 316).

Table 2. — **Comorbidities in patients from Belgium with HCV infection prior to initiating treatment with a second-generation direct-acting antiviral regimen (occurring in >5% of all patient population)**

	EBR/GZR	OBV/PTVr	SOF +	LED/SOF	SOF/VEL	All
Comorbidities	**± RBV**	**±DSV± RBV**	**DAC ± RBV**	**± RBV**	**± RBV**	**Patients**
(MeDRA term), *n* (%)	***N*=111**	***N*=34**	***N*=107**	***N*=27**	***N*=126**	***N*=405**
Hypertension	24 (21.6)	18 (52.9)	21 (19.6)	14 (51.9)	33 (26.2)	110 (27.2)
HIV coinfection	16 (14.4)	3 (8.8)	33 (30.8)	11 (40.7)	28 (22.2)	91 (22.5)
T2DM	20 (18.0)	7 (20.6)	13 (12.1)	6 (22.2)	12 (9.5)	58 (14.3)
Dependence	14 (12.6)	2 (5.9)	12 (11.2)	2 (7.4)	24 (19.0)	54 (13.3)
Depression	19 (17.1)	5 (14.7)	8 (7.5)	4 (14.8)	17 (13.5)	53
Gastrointestinal disorder	15 (13.5)	3 (8.8)	7 (6.5)	5 (18.5)	14 (11.1)	44 (10.9)
Anxiety	4 (3.6)	3 (8.8)	8 (7.5)	2 (7.4)	13 (10.3)	30 (7.4)
Thrombocytopenia	7 (6.3)	0 (0)	9 (8.4)	2 (7.4)	10 (7.9)	28 (6.9)
Dyslipidemia	6 (5.4)	2 (5.9)	1 (0.9)	0 (0)	15 (11.9)	24 (5.9)

DAC, daclatasvir ; DSV, dasabuvir ; EBR, elbasvir ; GZR, grazoprevir ; HCV, hepatitis C virus ; HIV, human immunodeficiency virus ; LED, ledipasvir ; MedDRA, Medical Dictionary for Regulatory Activities ; OBV, ombitasvir ; PTVr, paritaprevir/ritonavir ; RBV, ribavirin ; SOF, sofosbuvir ; T2DM, type 2 diabetes mellitus.

Table 3. — **Concomitant medications in patients from Belgium with HCV infection prior to initiating treatment with a second-generation direct-acting antiviral regimen (occurring in >10% of all patient population)**

	EBR/GZR	OBV/PTVr	SOF +	LED/SOF	SOF/VEL	All
Concomitant	**± RBV**	**±DSV± RBV**	**DAC ± RBV**	**± RBV**	**± RBV**	**Patients**
Medication, *n* (%)	***N*=111**	***N*=34**	***N*=107**	***N*=27**	***N*=126**	***N*=405**
Psycholeptics	26 (23.4)	9 (26.5)	32 (29.9)	7 (25.9)	42 (33.3)	116 (28.6)
Antivirals for systemic use	17 (15.3)	4 (11.8)	36 (33.6)	12 (44.4)	29 (23.0)	98 (24.2)
Drugs for acid-related disorders	30(27.0)	9 (26.5)	13 (12.1)	6 (22.2)	27 (21.4)	85 (21.0)
Agents acting on the renin-angiotensin system	22 (19.8)	7 (20.6)	16 (15.0)	12 (44.4)	26 (20.6)	83 (20.5)
Beta-blocking agents	17 (15.3)	10 (29.4)	14 (13.1)	6 (22.2)	24 (19.0)	71 (17.5)
Anti-thrombotic agents	22 (19.8)	7 (20.6)	10 (9.3)	8 (29.6)	20(15.9)	67 (16.5)
Drugs used in diabetes	18 (16.2)	8 (23.5)	15 (14.0)	7 (25.9)	12 (9.5)	60 (14.8)
Psychoanaleptics	21 (18.9)	7 (20.6)	13 (12.1)	4 (14.8)	14 (11.1)	59 (14.6)
Lipid-modifying agents	11 (9.9)	3 (8.8)	8 (7.5)	4 (14.8)	21 (16.7)	47 (11.6)
Analgesics	20 (18.0)	4 (11.8)	6 (5.6)	3 (11.1)	13 (10.3)	46 (11.4)
Calcium-channel blockers	10 (0.9)	8 (23.5)	8 (7.5)	7 (25.9)	13 (10.3)	46 (11.4)
Vitamins	16 (14.4)	2 (5.9)	7 (6.5)	3 (11.1)	18 (14.3)	46 (11.4)
Diuretics	11 (9.9)	4 (11.8)	6 (5.6)	8 (29.6)	12 (9.5)	41 (10.1)

DAC, daclatasvir ; DSV, dasabuvir ; EBR, elbasvir ; GZR, grazoprevir ; HCV, hepatitis C virus ; LED, ledipasvir ; OBV, ombitasvir ; PTVr, paritaprevir/ritonavir ; RBV, ribavirin ; SOF, sofosbuvir.

and 1 patient with F2 fibrosis started OBV/PTV/r ± DSV in 2016) and 405 were included in the final analysis population (Figure 1).

One hundred and eleven patients (27.4%) received EBR/GZR, 34 (8.4%) received OBV/PTVr ± DSV, 107 (26.4%) received SOF + DAC, 27 (6.7%) received SOF/LED, and 126 (31.1%) received SOF/VEL. For 289 patients (71.4%), the most recent DAA treatment was administered without ribavirin and 116 patients (28.6%) received ribavirin as part of their HCV treatment regimen (Table 1). In the overall study population, 60.6% (245/405) of patients were male and mean age was 56 years (SD, 13.4 years ; range, 24-90 years). Overall, 29.7% had HCV genotype (GT) 1b infection, 27.7% had GT1a infection, and 19.8% had GT4 infection. Patients with GT3 infection (n = 61) received SOF + DAC (n = 33) or SOF/VEL (n = 28). EBR/GZR, OBV/PTVr ± DSV, and SOF/LED were used primarily in the treatment of patients with HCV GT1 or GT4 infection. While 55.8% of patients had mild-moderate F0-F2 liver fibrosis, 23.7% had F3 fibrosis and 20.5% had Child-Pugh A cirrhosis (Table 1).

Comorbidities and concomitant medications

A total of 956 comorbidities were reported by 362 patients (median, 2 comorbidities per patient ; range,

Table 4. — **Comorbidities and concomitant medications among specific patient subgroups**

	HIV Coinfection Status		Age		Cirrhosis Status	
	HCV Monoinfection	**HCV/HIV Coinfection**	**Age <65 years**	**Age ≥65 years**	**Noncirrhotic**	**Cirrhotic**
	***n* = 314**	***n* = 314**	***n* = 301**	***n* = 104**	***n* = 322**	***n* = 83**
Comorbidities, median (range)	2 (0-15)	1 (1-7)	1 (0-15)	3 (0-15)	2 (0-15)	2 (0-15)
Most common comorbidities	Hypertension (30.6%) Type 2 diabetes mellitus (18.2%) Dependence (16.6%)	HIV infection (100%) Hypertension (15.4%) Depression (12.1%)	HIV infection (29.2%) Hypertension (17.3%) Dependence (15.9%)	Hypertension (55.8%) Type 2 diabetes mellitus (27.9%) Gastrointestinal disorder (20.2%)	HIV infection (26.7%) Hypertension (25.5%) Type 2 diabetes mellitus (12.7%)	Hypertension (33.7%) Thrombocytopenia (22.9%) Type 2 diabetes mellitus (20.5%)
Concomitant medications, median (range)	3 (0-16)	3 (1-12)	2 (0-16)	5 (0-15)	3 (0-16)	3 (0-16)
Most common concomitant medications	Psycholeptics (30.9%) Drugs for acid-related disorders (24.8%) Agents acting on the reninangio-tensin system (23.2%)	Antivirals (100%) Psycholeptics (20.9%) Vitamins (12.1%)	Antivirals (31.2%) Psycholeptics (28.2%) Drugs for acid-related disorders (14.3%)	Agents acting on the reninangio-tensin system (45.2%) Antithrombotic agents (42.3%) Drugs for acid-related disorders (40.4%)	Antivirals (28.6%) Psycholeptics (28.6%) Drugs for acid-related disorders (20.2%)	Psycholeptics (28.9%) Beta blockers (28.9%) Drugs for acid-related disorders, agents acting on the reninangiotensin system, and anti-thrombotic agents (24.1%, each)

0-15) (Table 2). The most common comorbidities across all patients were hypertension (*n* = 110, 27.2%) ; HIV coinfection (*n* = 91, 22.5%), and type 2 diabetes mellitus (*n* = 58, 14.3%).

Overall, 1455 concomitant medications were being taken by 365 patients (90.1%, 365/405) (median of 3 concomitant medications per patient ; range, 0–16). The most common therapeutic classes of concomitant medications were psycholeptics (n = 116, 28.6%), systemic antiviral agents (*n* = 98, 24.2%) and medications for acid-related disorders (n = 85, 21.0%) (Table 3). Overall, 74 of 365 (20.3%) patients who were receiving a concomitant medication required an adaptation to their concomitant medication. Among these 74 patients, 31 (7.5%) changed a concomitant medication (ie, change in dose, timing, or frequency, or switch to another drug), 51 (14.0%) stopped at least one concomitant medication, and 8 both stopped and changed a concomitant medication. The medications that most frequently required change were drugs used for acid-related disorders (*n* = 14) and antiviral drugs (*n* = 5) ; those that were most frequently stopped were lipid-modifying drugs (*n* = 25) and drugs for acid-related disorders (*n* = 13).

The frequency of comorbidities and concomitant medications was higher in patients aged ≥65 years compared with younger patients but did not vary according to cirrhosis status or HIV coinfection status (Table 4). Specific comorbidities and concomitant medications were generally similar, regardless of coinfection status, age, or presence of cirrhosis. HIV infection and antiviral medications were common among the younger and noncirrhotic populations, and the sequelae of liver cirrhosis were apparent with a higher proportion of cirrhotic patients reporting comorbid thrombocytopenia, or receiving beta blockers or antithrombotic agents (Table 4).

Change in concomitant medications prior to starting HCV treatment

There was a decline in the number of patients considered at risk for a DDI between HCV diagnosis and initiation of HCV therapy (Figure 2). At diagnosis, 34% of patients (136/405) were considered at risk for a potentially clinically relevant DDI, of whom 125 were receiving a concomitant medication with a potential DDI to their planned HCV regimen and 11 were receiving a concomitant medication with a contraindication to their planned HCV treatment regimen. Of the 125 patients

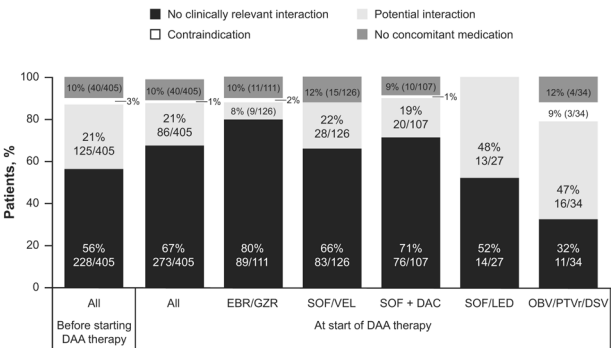

Figure 2. — Risk of potentially clinically relevant drug-drug interactions in patients with HCV infection at initiation of second-generation direct-acting antiviral medication. DAA, direct-acting antiviral agents ; DAC, daclatasvir ; DSV, dasabuvir ; EBR, elbasvir ; GZR, grazoprevir ; HCV, hepatitis C virus ; LED, ledipasvir ; OBV, ombitasvir ; PTVr, paritaprevir/ritonavir ; SOF, sofosbuvir ; VEL, velpatasvir.

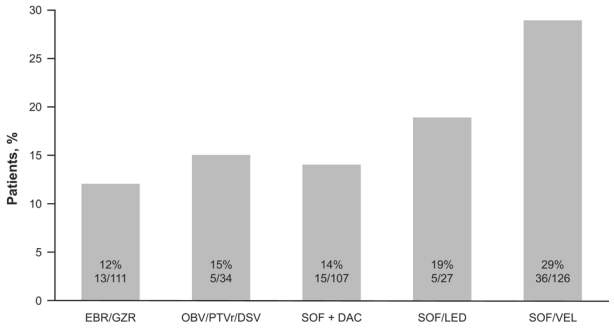

Figure 3. — Requirement for modification of concomitant medications in patients with HCV infection at initiation of second-generation direct-acting antiviral medication. DAC, daclatasvir ; DSV, dasabuvir ; EBR, elbasvir ; GZR, grazoprevir ; HCV, hepatitis C virus ; LED, ledipasvir ; OBV, ombitasvir ; PTVr, paritaprevir/ritonavir ; SOF, sofosbuvir ; VEL, velpatasvir.

with a potential DDI to their planned HCV regimen, 86 patients remained at risk for a potential DDI at the time of initiating DAA therapy. Similarly, of the 11 patients receiving a concomitant medication with a contraindication to their planned HCV regimen, 5 continued to have a known contraindication at the time of HCV treatment initiation. Overall, the number of patients considered at risk for a DDI declined from 136 at diagnosis to 91 at the start of HCV treatment, suggesting that concomitant drug modifications were effective in removing the risk of a DDI in 45 patients.

At the time of HCV treatment initiation, the risk of potential DDIs varied according to treatment regimen (Figure 2). The risk of DDI was lowest in patients initiating HCV treatment with EBR/GZR (10% ; 11/111), SOF + DAC (20% ; 21/107), or SOF/VEL (22% ; 28/126) and highest in those receiving SOF/LED (48% ; 13/27) or OBV/PTVr ± DSV (56% ; 19/34) (overall $P < 0.0001$). The proportion of patients with no identified clinically relevant DDI between concomitant medication and HCV regimen at the time of starting HCV treatment was highest in those initiating treatment with EBR/GZR (80% ; 89/111) and lowest in those initiating treatment with OBV/PTVr ± DSV (32% ; 11/34) (Figure 2).

Twenty-nine percent of patients initiating SOF/VEL underwent dose modification of their concomitant medications prior to initiating HCV therapy compared with 12% of those initiating EBR/GZR, 14% of those initiating SOF + DAC, 15% of those initiating OBV/PTVr ± DSV, and 19% of those initiating SOF/LED ($P <0.0010$, corrected for multiple testing) (Figure 3).

Discussion

Data from this study provide insight into the comorbidities and concomitant medications frequently encountered in patients initiating DAA therapy for chronic HCV infection in Belgium. Most patients included in this analysis were treatment-naive with HCV GT1, GT3, or GT4 infection : ~44% had bridging fibrosis or cirrhosis, ~22% were HIV coinfected and ~26% were aged ≥65 years. The most common comorbidities were hypertension, HIV coinfection, and type 2 diabetes mellitus, and the most common concomitant medication classes were psycholeptics, antivirals, and drugs for acid-related disorders. Comorbidities and concomitant medications generally did not vary according to HIV coinfection status, age, or presence of cirrhosis, although the frequency of both comorbidities and concomitant medications tended to be higher among patients aged ≥65 years.

Our data indicate that changes in concomitant medications prior to initiating HCV treatment reduced the risk of DDIs. Across the various treatment regimens studied, changes in dosing prior to initiation of DAA therapy were lowest among patients receiving EBR/GZR and OBV/PTVr ± DSV and higher among those receiving SOF/LED or SOF/VEL. Although contradictory that OBV/PTVr ± DSV has the highest risk for DDIs but dosing modifications were among the lowest could be found in the fact that physicians were predisposed to use sofosbuvir-based regimens (eg. patients on HIV treatment) since it is know that with certain dose modifications HCV and HIV treatment can be given together. While this is not possible for OBV/PTVr ± DSV treatment.

Among patients receiving EBR/GZR, 12% had cirrhosis ; 7% were receiving concomitant ribavirin, and 14% had HIV coinfection. Thus, the population receiving EBR/GZR represented a generally healthy cohort, largely without the concomitant medications required by patients with HIV coinfection or cirrhosis. Similarly, only 9% of the population receiving OBV/PTVr ± DSV had HIV coinfection. In contrast, 41% of patients receiving SOF/LED had HIV coinfection and 44% were cirrhotic (at the time of the study, SOF/LED was reimbursed in Belgium only for patients with F3/F4 fibrosis) : this treatment group therefore represented a population that was more predisposed to DDIs through the higher frequency of comorbidities and associated concomitant medications. The potential for DDIs with each HCV treatment regimen was therefore influenced by the unique metabolic/pharmacokinetic properties of each regimen, by the status of drug approval/availability during the study, and by the differing characteristics of the patient populations enrolled to each regimen, reflecting treatment guidelines and prescribing practices in Belgium during the time of the study (6, 7).

Comorbidities and concomitant medications reported in the present study are generally consistent with those reported previously in individuals with HCV infection. Studies from Japan and the United States indicate that gastrointestinal disorders, hypertensive disorders, metabolic disorders, and diabetes mellitus are common among people with HCV infection (10). Likewise, concomitant medications reported in individuals with HCV infection were similar those reported elsewhere, with other studies noting high frequencies of people

with HCV infection receiving proton-pump inhibitors/antacids, angiotensin-2 antagonists, and statins (11). It is notable that approximately 30% of individuals with HCV infection are reported to use concomitant proton-pump inhibitors or another acid-reducing agent (12), and previous studies have shown that proton-pump inhibitors/histamine H2 receptor antagonists are one of the most likely drug classes to contribute to a DDI in patients undergoing DAA therapy for HCV infection, particularly in those with moderate-to-advanced liver fibrosis (13-17).

In this study, dose modifications of concomitant medications prior to initiation of DAA therapy resulted in a decline in the risk of potentially clinically relevant DDIs. Prior to adjustment of concomitant medications, 136 of 405 enrolled patients (34%) were considered at risk for a potentially clinically relevant DDI, whereas following adjustment, the number at risk for a DDI decreased to 91 of 405 (22%). The number of patients with a potential contraindication to their concomitant medication decreased from 11 at the time of DAA initiation to 5 at the start of treatment. Evaluation of potentially clinically relevant DDIs was performed in August 2018 using information from https://www.hep-druginteractions.org. For those data collected retrospectively (collection period of 2015-2016), a substantial amount of time elapsed between clinical consideration of the potential for DDIs and the time at which the potential for a DDI was analyzed. It is therefore possible that DDIs identified at the time of analysis were not known or listed on www.hep-druginteractions.org at the time of clinical consultation. For example, initial data regarding the potential DDI between ledipasvir and proton-pump inhibitors was heavily refined during 2015 and 2016 and therefore was well documented at the time of analysis in this study but was likely less well established at the time of clinical presentation (18, 19). The elapsed time between medication adaptation and analysis may therefore partly explain why potential DDIs were not completely resolved prior to DAA therapy initiation ; however, it is also likely that lack of physician awareness concerning the potential for DDIs with HCV medications also contributed to the fact that 22% of patients initiated HCV treatment while taking a concomitant medication with potential for a DDI. Clinical outcomes data were not collected in this study and therefore the consequences of DDIs (if any) and their clinical relevance cannot be determined.

The individual HCV treatment regimens each have a unique DDI profile. Coadministration of EBR/GZR with acid-reducing agents has no clinically relevant impact on the pharmacokinetics of EBR/GZR, and rates of sustained virologic response are unaffected in patients with HCV infection receiving EBR/GZR and concomitant proton-pump inhibitor therapy (20, 21). There is also no clinically relevant impact on EBR/GZR exposure when EBR/GZR is coadministered with oral contraceptive agents or opioid agonist therapies (22-24). Drug-drug interactions have been reported between EBR/GZR and certain antiretroviral therapies for HIV infection. Increased GZR exposure has been reported when EBR/GZR is coadministered in combination with the fixed-dose combination of elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine (25) or with the ritonavir-boosted protease inhibitors atazanavir, lopinavir, and darunavir (26, 27). Ledipasvir and velpatasvir have pH-dependent solubility, and therefore concomitant use of agents that increase gastric pH, such as proton-pump inhibitors and histamine H2 receptor antagonists, can reduce their bioavailability (28). Studies also suggest that twice-daily concomitant proton-pump inhibitor use in patients receiving SOF/LED can result in lower rates of sustained virologic response (18). Fewer drug interactions exist between SOF/LED or SOF/VEL and antiretroviral medications. Regimens based on tenofovir-boosted protease inhibitors should be avoided in patients receiving SOF/LED or SOF/VEL (30, 31). OBV/PTVr ± DSV is perhaps the HCV treatment regimen most predisposed to DDIs with concomitantly administered agents (1). This regimen should be avoided in patients with HIV coinfection receiving non-nucleoside reverse transcriptase inhibitors and several boosted protease inhibitors. There are also potential interactions with some illicit/recreational drugs, lipid-lowering agents, and central nervous system and cardiovascular drugs (1). Physicians should consult prescribing information for detailed guidance on dosing adjustments for all HCV treatment regimens (27, 29-31).

The present study is subject to some limitations. The patient population enrolled in this study was heavily influenced by the reimbursement criteria for HCV medication in Belgium prior to January 2019 (7), particularly patients with more advanced liver disease (liver fibrosis stage ≥ F2) or those from high-risk groups such as patients with HIV coinfection. These reimbursement criteria to some extent therefore explain the small proportion of patients with F0-F1 liver fibrosis (15%) and the relatively high proportion of those with HIV coinfection (22%) enrolled in this study. At the time of the study, reimbursement for HCV therapies was available to all patients with HIV coinfection, irrespective of the degree of fibrosis, whereas, for non–HIV coinfected patients, reimbursement was only available to those with F3-F4 fibrosis (availability was expanded to patients with F2 fibrosis in January 2017). In January 2019, reimbursement access was expanded to all patients in Belgium, irrespective of fibrosis stage, a strategy that is forecast to aid in meeting World Health Organization targets for the care and management of HCV infection (32). The treatment landscape for HCV infection has also changed since the time of this study and therefore the data do not reflect current treatment options such as the more recent availability of glecaprevir/pibrentasvir and SOF/VEL/voxilaprevir. The prospective and retrospective parts of the study may also represent a source of bias. Data from patients with F3/

F4 fibrosis receiving treatments other than EBR/GZR and SOF/VEL were collected retrospectively, possibly limiting meaningful comparisons between the older (SOF/LED, OBV/PTVr ± DSV, SOF + DAC) and newer treatments (EBR/GZR and SOF/VEL). Retrospective data were collected between 2015 and 2016, whereas the prospective data were collected from January 2017 onwards. Retrospective data from patients with F3-F4 fibrosis may also include a higher proportion of complications and comorbidities arising from the more advanced liver disease in this population. Comparisons of the retrospective and prospective data from patients with F3/F4 fibrosis therefore should be interpreted with caution.

Conclusion

In conclusion, this is the first study to describe the modification of concomitant medications in patients from Belgium initiating treatment with a second-generation DAA regimen. In this study, most patients (90%) were receiving concomitant medications prior to initiation of HCV treatment and in ~20% of patients, concomitant medications were adjusted/modified prior to starting HCV treatment. Nevertheless, at the time of HCV treatment initiation, ~22% of patients remained at risk for a potentially clinically relevant DDI. This study suggests that physicians are aware of the potential for DDIs between concomitant medications and DAAs but that improved alignment between clinical practice and theoretical recommendations is still required.

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Conflicts of interest and sources of funding

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Author Contributions

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Analysis of the data : SB, IC, CVS, SHC, KV, TV, JPM

Interpretation of the results : SB, MRC, XV, GKMMR, LL, IC, CVS, JD, SHC, KV, TV, JPM, VL

Drafting of the manuscript : SB, GKMMR, SHC, TV

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