Drug-drug interactions in HCV therapy: Still relevant for clinical practice?

Benjamin Schulte[1,3], Maximilian Wübbolding[1], Kerstin Port[1], Michael P. Manns[1,3], David Back[2], Fiona Marra[2], Markus Cornberg[1,3], Benjamin Maasoumy[1,3], Christoph Höner zu Siederdissen[1]

[1]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Carl-Neuberg-Straße 1, 30625 Hannover, Germany
[2]University of Liverpool, Molecular and Clinical Pharmacology, Liverpool L69 3BX, United Kingdom
[3]German Centre for Infection Research (Deutsches Zentrum für Infektionsforschung DZIF), Partner-site Hannover-Braunschweig, Hannover, Germany

Background:

- With direct-acting antivirals (DAA) drug-drug interactions (DDI) have emerged as a new challenge in the treatment of hepatitis C virus infection (HCV).
- Pharmacokinetic DDI can lead to either higher rates of adverse events or decreased rates of sustained virological response (SVR).

Aim:

- In the present study we aimed to i) assess if the frequency of DDI has changed over time, ii) identify patients with an increased risk for DDI, iii) identify drugs most commonly involved and iv) look at relevant DDI mechanisms.

Patients and Methods:

- In total 668 HCV patients treated at Hannover Medical School from January 2014 to July 2018 were evaluated for their concomitant medications.
- Herbal drugs and nutritional supplements containing several (active) ingredients were only counted as one medication. In case of other combination preparations, e.g. sitagliptin/metformin, each active ingredient was counted separately.
- If concomitant medications were changed prior to HCV treatment due to suspected DDI the initially used concomitant medications were included in the analysis.
- DDI were classified as follows: 1) no interaction expected, 2) potential weak interaction, 3) potential significant interaction and 4) do not coadminister.
- To evaluate changing frequencies of DDI over time with various DAA regimens, periods were defined as follows: A) January 2014 – November 2014, B) November 2014 – August 2016 and C) August 2016 – July 2018, based on new approval of key DAA.
- The assessment was based on data from hep-druginteractions.org, in case of missing information an expert opinion of a pharmacist and Prescribing Information.

Table 1 Baseline characteristics of the study cohort — n/a: not available

	Total cohort	Jan. 2014 – Nov. 2014	Nov. 2014 – Aug. 2016	Aug. 2016 – Jul. 2018
Number of patients (n, %)	**668 (100.0)**	162 (24.3)	256 (38.3)	250 (37.4)
Sex (n, %)				
female	**301 (45.1)**	65 (40.1)	122 (47.7)	114 (45.6)
male	**367 (54.9)**	97 (59.9)	134 (52.3)	136 (54.4)
Age (years; mean, range)	**55.5 (18 – 85) [6.6% >74 years]**	55.3 (24 – 81)	58.2 (24 – 85)	52.9 (18 – 82)
Cirrhosis (n, %)	**282 (42.2)**	120 (74.1)	105 (41.0)	57 (22.8)
Hepatitis C virus genotype (n, %)				
1	**477 (71.4)**	101 (62.3)	217 (84.8)	159 (63.6)
2	**29 (4.3)**	13 (8.0)	2 (0.8)	14 (5.6)
3	**123 (18.4)**	42 (25.9)	23 (9.0)	58 (23.2)
4	**22 (3.3)**	4 (2.5)	7 (2.7)	11 (4.4)
5	**7 (1.0)**	1 (0.6)	2 (0.8)	4 (1.6)
6	**1 (0.1)**	0 (0)	0 (0)	1 (0.4)
n/a	**9 (1.3)**	1 (0.6)	5 (2.0)	3 (1.2)

- The median of home medications per patient in the total cohort was 3 (range: 0-19).

Results (in %):

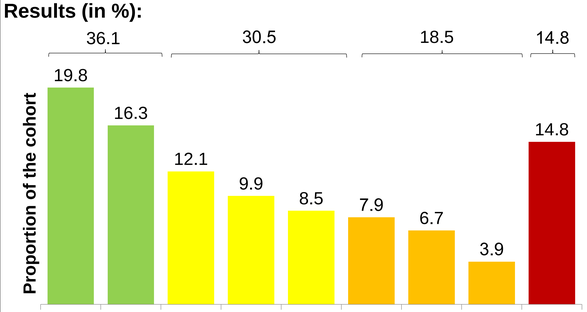

Figure 1 Number of drugs in the home medication at baseline

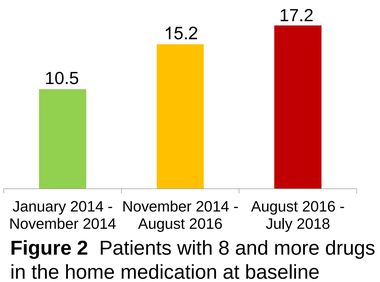

Figure 2 Patients with 8 and more drugs in the home medication at baseline

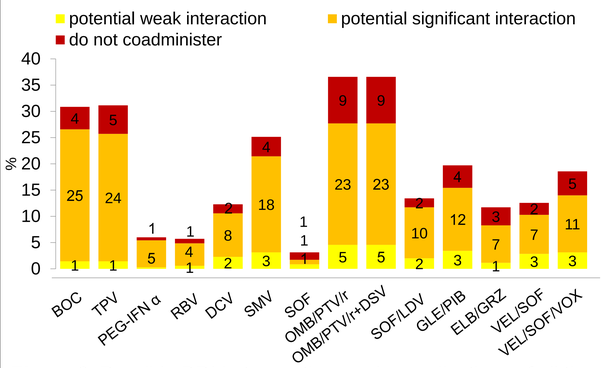

Figure 3 Possible DDI between the regular medications of all the patients and different DAA regimens

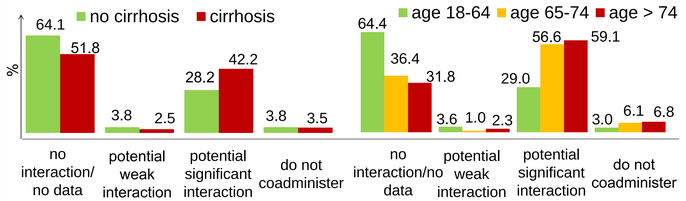

Figure 5 Proportion of patients affected by significant DDI between their regular medication and the used HCV regimen depending on the presence of cirrhosis and age at baseline

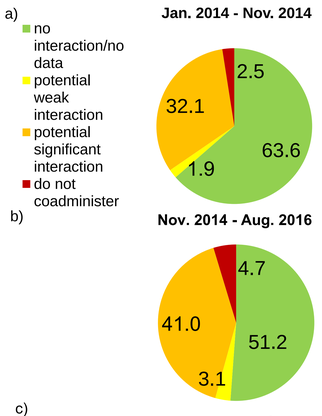

Figure 4 Proportion of patients affected by significant DDI between their regular medication and the used HCV regimen in different time periods at baseline

Conclusions:

- **DDI affect ~40 % of patients even with modern DAA**
- **Polypharmaceutical patients are an increasing subgroup and need to be kept in mind as high risk patients for DDI**
- **Of note, number of cirrhotic patients and older patients decreases**
- **DDI mechanisms differ between the DAA regimen**

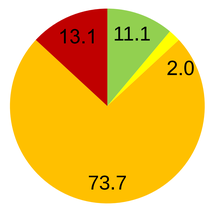

Figure 6 Proportion of patients affected by signigicant DDI between their regular medication and used HCV regimen for patients with 8 and more drugs in home medication at baseline

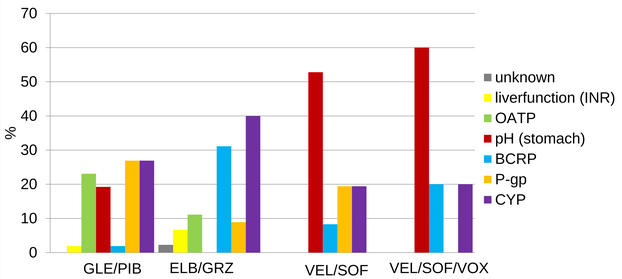

Figure 7 Mechanisms of DDI occuring between regular medication and HCV regimen in the time period Aug. 2016 – Jul. 2018

Key results:

- Frequency of polypharmacy has been increasing (Fig. 1/2)
- Theoretically modern regimens have a lower DDI potential (Fig. 3)
- Proportion of patients affected by DDI remains stable (Fig. 4)
- Cirrhosis, age and number of home medications are risk factors for DDI (Fig. 5/6)
- ELB/GRZ interacts mainly via CYP and BCRP (Fig. 7)
- VEL/SOF±VOX interacts mainly via increased pH value in the stomach and decreased bioavailability of Velpatasvir (Fig. 7)
- From 350 different regular medications DDI with modern regimens are common with proton pump inhibitors, metamizole, statins and carvedilol

Corresponding author: schulte.benjamin@mh-hannover.de

Poster presented at: EASL The International Liver Congress 2019

DOI: 10.3252/pso.eu.ILC2019.2019

Viral hepatitis Benjamin Schulte

THU-178

ILC2019