Concomitant drug use in patients with chronic hepatitis C and change over time: a nationwide population-based register study from 2005 through 2013

Jonas Söderholm[1,2], Ola Weiland[3], Alma Brolund[1], Jan Kövamees[1], Matthew Baartz[4], Anders Nystedt[5], and Katharina Büsch[1,2]

[1]AbbVie AB, Stockholm, Sweden, [2]Department of Laboratory Medicine, Division of Clinical Microbiology, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden, [3]Department of Medicine Huddinge, Division of Infectious Diseases, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, [4]AbbVie Pty Ltd, Sydney, Australia, [5]Center for Communicable Disease Control, Region Norrbotten, Sweden

Presented at the International Liver Congress 2018 by the European Association for the Study of the Liver, April 11 – 15, Paris, France

THU-333

BACKGROUND

Around 80% of patients infected with the hepatitis C virus will develop a chronic liver infection. Patients with chronic hepatitis C (CHC) have a significantly higher number of comorbidities compared with a comparator cohort (Büsch *et al*. 2017; Louie *et al*. 2012). The higher number of comorbidities most likely explains why patients with CHC use a greater number of concomitant drugs compared with undiagnosed controls (Juneja *et al*. 2013).

The approval of interferon-free direct-acting antivirals (DAAs) has improved the treatment of patients with CHC; however, but concomitant drug use may cause potential drug-drug interactions (DDIs). A recent real-world report from Italy indicated that 20% to 25% of the treated CHC patients taking concomitant drugs classified as having a risk for "potential interaction" which might require dose adjustment, and up 3% were prescribed a contraindicated drug (Kondili *et al*. 2017).

The aim of this nationwide registry study was to describe the utilization of prescribed drugs in all patients diagnosed with CHC in Sweden.

METHODS

Table 1. Description of National Patient Swedish Registers

Register	Description
National Patient Register	Contains all inpatient and non-primary outpatient care visits, such as treatment visits to an infectious disease specialist or gastroenterologist, but no primary care data. Available register data from: Inpatient care, 1987–2013; Day surgery, 1997–2000; and Non-primary outpatient care, 2001–2013 (including day surgery). It includes information on main and contributory diagnoses based on the *International Classification of Diseases* (ICD-9, 1987–1996; ICD-10, 1997-2013).
Prescribed Drug Register	Registers all dispensed prescribed drug use in ambulatory care using Anatomical Therapeutic Chemical (ATC) codes. This register retains information on dates, drugs, and costs for all pharmacy dispensations of prescriptions in Sweden (July 1, 2005, to 31st December, 2013). The coverage is complete for prescriptions in ambulatory care, while in-hospital use of drugs is captured to a lesser extent.

DISCLOSURES

JS, AB, JK, MB, and KB are or were employees of AbbVie and may hold stocks or stock options. AN has received honoraria for advisory boards/lectures from Abbvie, MSD, and Gilead and has received research support from AbbVie. OW has consultancies with AbbVie, BMS, Gilead, Janssen, Medivir, Roche, and MSD/Merck, and has worked on speaker bureaus for AbbVie, BMS, Gilead, Janssen, Medivir, Roche, and MSD/Merck.

The design, study conduct, and financial support for the study were provided by AbbVie. AbbVie participated in the study design, data analysis, interpretation of results, review, and approval of the publication. The authors determined the final content. No payments were made to the authors for writing this publication.

OBJECTIVES

- Describe potential DDIs during a calendar year according to theoretically prescribed DAAs.
- Describe the number of potential DDIs with prescribed drugs in CHC patients over time.
- Evaluate the impact of the number drugs used on survival.

METHODS

SETTING

In Sweden, universal access to healthcare is provided to the population through a tax-funded system. Patients with CHC are typically cared for by specialists in infectious diseases or gastroenterology in hospital-based outpatient clinics or inpatient facilities. They are not managed by general practitioners in primary care (Büsch *et al* 2017).

DATA SOURCES

Register sources included the National Patient Register and the Prescribed Drug Register, all kept by the Swedish National Board of Health and Welfare (**Table 1**). The Swedish nationwide registers were used to identify patients with CHC using the *International Classification of Diseases*, 10th revision (ICD-10) code B18.2, and dispensed drug utilization. Data on place of residence, vital statistics, and emigration status were retrieved from the Register of the Total Population held by Statistic Sweden (up to December 31, 2013). This register covers the entire Swedish population and includes information on age, sex, and place of residence as well as dates of birth, and emigration status. Information regarding death was retrieved from the Cause of Death registry. The Swedish personal identity number (social security number) was used to link individuals between registers.

Drugs specific for the treatment of hepatitis C (telaprevir, boceprevir, ribavirin, and interferon-α) were excluded from all analyses.

The study was approved by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden.

ABBREVIATIONS

ATC – Anatomical Therapeutic Chemical; **CI** – confidence interval; **CHC** – chronic hepatitis C; **DAA** – direct acting antiviral; **DSV** – dasabuvir; **EBR/GZR** – elbasvir/grazoprevir; **ICD** – International Classification of Diseases; **IFN** – interferon; **GLE/PIB** – glecaprevir/pibrentasvir; **LDV** – ledipasvir; **OBV/PTV/r** – ombitasvir/paritaprevir/ritonavir; **SOF** – sofosbuvir; **VEL** – velpatasvir; **VOX** – voxilaprevir.

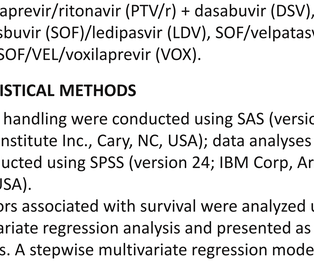
REFERENCES

AbbVie Ltd, 2017. Viekirax (ombitasvir/paritaprevir/ritonavir). Summary of Product Characteristics. Maidenhead, UK; AbbVie Ltd, 2018. Maviret (glecaprevir/pibrentasvir). Summary of Product Characteristics. Maidenhead, UK Büsch K, *et al*. Scand J Gastroenterol. 2017;52(1):61-68.; Gilead, 2017:1. Harvoni (ledipasvir/sofosbuvir). Summary of Product Characteristics. Cambridge, UK; Gilead, 2017:2. Epclusa (sofosbuvir/velpatasvir). Summary of Product Characteristics. Cambridge, UK; Hep Drug, 2018, www.hep-druginteractions.org. Accessed March 22, 2018; Louie KS, *et al*. BMC Infect Dis. 2012;12:86; Juneja M, *et al*. Dig Dis Sci. 2013;58:3348-3358; Kondili LA, *et al.* PLoS One. 2017;12(2):e0172159.

RESULTS

As of December 31, 2013, there were 34,633 patients with a CHC diagnosis living in Sweden, of which 84.5% (n=29,266) had at least one dispensed prescription drug. In total there were 59 different drugs with "*do not co-administer*" to at least one DAA. The most common contraindicated drug to GLE/PIB, OBV/PTV/r+DSV, and SOF/VEL/VOX regimens was simvastatin (4.9% of patients), and the most common contraindicated drug to EBR/GZR, LDV/SOF, and SOF/VEL was carbamazepine (2.0% of patients; **Table 2**).

Fig 1. Percentage of DDI classifications* for all dispensed drugs in 2013 per DAA.



*The Hep Drug iChart has not updated the DDI interaction between GLE/PIB and omeprazole according the latest update of the Summary of Product Characteristics for GLE/PIB (AbbVie 2018), i.e., the proportion of amber interactions for GLE/PIB is overestimated.

METHODS (CONTINUED)

OBSERVATION TIME

All living patients diagnosed with CHC as of December 31, 2013 (previously described in Büsch *et al*. [2017]), were used to analyze concomitant drug use in 2013. The longitudinal analysis of the number of concomitant drugs after CHC diagnosis only included patients diagnosed after July 1, 2005 (i.e., since the inception of the Prescribed Drug Register), and only patients with a full year of follow-up were included at each year. The observation time ended at the time of death, emigration, or December 31, 2013, whichever came first.

ASSESSMENTS OF POTENTIAL DDIs

The potential for DDI interactions was assessed using the HEP Drug iChart (University of Liverpool, UK; date: March 22, 2018) for elbasvir (EBR)/grazoprevir (GZR), glecaprevir (GLE)/pibrentasvir (PIB), ombitasvir (OBV)/ paritaprevir/ritonavir (PTV/r) + dasabuvir (DSV), sofosbuvir (SOF)/ledipasvir (LDV), SOF/velpatasvir (VEL), and SOF/VEL/voxilaprevir (VOX).

STATISTICAL METHODS

Data handling were conducted using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA); data analyses were conducted using SPSS (version 24; IBM Corp, Armonk, NY, USA).

Factors associated with survival were analyzed using a univariate regression analysis and presented as odds ratios. A stepwise multivariate regression model was used to assess for factors that were independently associated with survival. A Kaplan-Meier survival curve was performed to visualize survival over time using a log-rank test . All reported *P*-values are two-sided.

On average, each patient with a prescription was dispensed 7 different drugs during 2013. Paracetamol and omeprazole were the two most commonly used drugs, used by 21% and 18% of all patients respectively. According to the Liverpool HEP iChart database, none of the 10 most commonly prescribed drugs for patients with CHC in 2013 were classified as "*do not co-administer*" (data not shown).

The percentage of drugs used in all patients in 2013 classified for each DAA according to the iChart database is shown in **Fig. 1**. Most drugs used in the real world are considered safe from a DDI perspective. Between 1% to 2% of the cases were classified as "*do not co-administer*" for most combinations, with the exception being OBV/PTV/r+DSV (6%). Between 3% to 9% of the combinations were classified as "*potential interaction*", with the exception of OBV/PTV/r+DSV (23%).

Table 2. Top 10 Most Commonly Prescribed Drugs in 2013 With a "*Do Not Co-administer*" Classification to Any DAA.

Drugs	N (%)	EBR/GZR	LDV/SOF	GLE/PIB	OBV/PTV/r+DSV	SOF/VEL	SOF/VEL/VOX
Simvastatin	1695 (4.9)						
Mometasone (Inhalant)	1582 (4.6)						
Formoterol & budesonide	1272 (3.7)						
Budesonide (Inhalant)	1249 (3.6)						
Quetiapine	1198 (3.5)						
Mometasone (Topical)	822 (2.4)						
Carbamazepine	705 (2.0)						
Atorvastatin	457 (1.3)						
Budesonide (Topical)	406 (1.2)						
Alfuzosin	398 (1.1)						

DDI classification as of March 22, 2018 (Hep Drug 2018)

LONGITUDINAL ANALYSIS

In order to investigate drug use over time following CHC diagnosis, we analyzed the changes in the number of different used drugs between year 1 to year 2 for all patients with two full years of follow-up (n=15,992). Forty-five percent used fewer drugs year 2, 18% used the same number, and 37% used an increased number of drugs in year 2 (**Fig. 2**). We also analyzed the number of different drugs used by the patients during each year after CHC diagnosis. The reduced number of drugs used from year 1 to year 2 seemed to be stable over time (**Fig. 3**).

Fig 2. Changes in the number of different drugs dispensed in 2013 for patients with CHC (n=15,992).

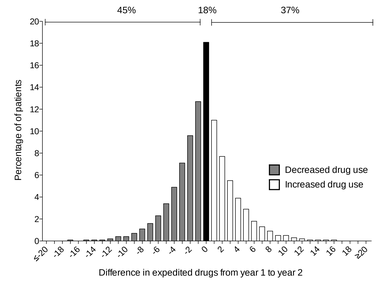
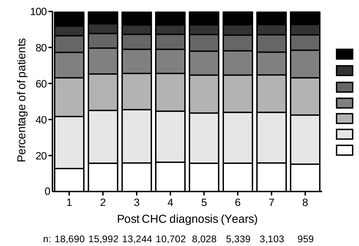


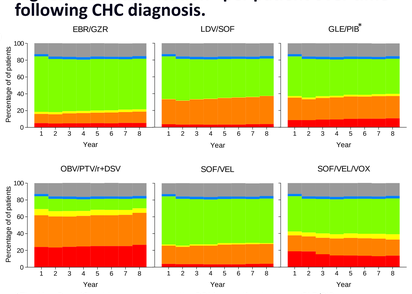
Fig 3. Proportion of different drugs during each year after CHC diagnosis



LONGITUDINAL ANALYSIS (CONTINUED)

Figure 4 shows the proportion of patients according to the highest potential DDI per each DAA up to 8 years after CHC diagnosis.

Fig 4. Percentage of patients according to the highest DDI classification* per patient over time following CHC diagnosis.



*The Hep Drug iChart has not updated the DDI interaction between GLE/PIB and omeprazole according the latest update of the Summary of Product Characteristics for GLE/PIB (AbbVie 2018), i.e., the proportion of amber interactions for GLE/PIB is overestimated.

SURVIVAL

A lower number of drugs used was associated with a higher survival, as assessed using Kaplan-Meier analyses when the patients were grouped according to the number of drugs used during the first year after CHC diagnosis (0, 1-3, or ≥4 different drugs; **Fig. 5**).

A greater number of drugs used during year 1, increased drug use during year 2, male sex, and earlier birth years (i.e., older patients) were independently associated with mortality as analyzed using a stepwise multivariate regression analysis (**Table 3**).

Fig 5. Cumulative survival in patients with CHC grouped depending on the number of different drugs during year 1 after CHC diagnosis.

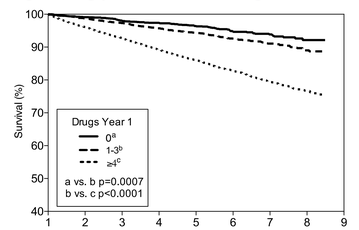


Table 3. Cumulative Survival in Patients With CHC Grouped According to the Number of Different Drugs Used During Year 1 Following CHC Diagnosis

	Univariate	95% CI	P-value	Multivariate	95% CI	P-value
Drugs year 1	1.079	1.070-1.089	P<0.0001	1.077	1.067-1.087	P<0.0001
Change in drugs to year 2	1.025	1.010-1.040	P=0.001	1.062	1.048-1.077	P<0.0001
Sex (male)	0.533	0.467-0.609	P<0.0001	0.442	0.384-0.508	P<0.0001
Birth year*	0.734	0.716-0.752	P<0.0001	0.766	0.746-0.786	P<0.0001

*=Five–years intervals from 1940 to 1990.

DISCUSSION

The majority of the drugs picked up by patients with CHC during 1 year do not have an expected interaction with any DAA, and only a fraction of the concomitant drugs were considered as "*do not co-administer*" with most of the currently available DAAs. The exception was the OBV/PTV/r+DSV combination, due to the inclusion of the protease-inhibitor booster ritonavir, which inhibits the CYP3A4 metabolic pathway (AbbVie 2017). The proportion of patients in each DDI classifications depending on DAA used was relatively stable over time after CHC diagnosis.

The most problematic concomitant medication was omeprazole, which was used by 18% of the patients and has clinical relevant interactions with LDV and VEL. For VEL, it is recommended that the dose of omeprazole be ≤20 mg and that VEL be administered 4 hours before omeprazole. For LDV, the recommendation is that LDV should not be administer after omeprazole (Gilead 2017:1 and 2). Of note, the Summary of Product Characteristics for Maviret was change in February 2018 to remove the restriction of GLE/PIB in combination with high dose omeprazole (AbbVie 2018), but as of April 3, 2018 the HEP Drug iChart has not yet updated the classification accordingly (Hep Drug 2018). The analyses maintains that old classifications for omeprazole provided by the HEP Drug iChart, i.e, the presented results will overestimate the proportion of drugs with potential interaction (amber) for GLE/PIB.

The highest number of different drugs was used during the first year after CHC diagnosis; the number of drugs used was already reduced during year 2. If patients with a more severe liver disease died earlier, this could have caused a selection bias in that mainly patients with mild liver disease were included at the later time points. On the other hand, only patients with two full years of follow-up were included. It is also possible that it was easier for physicians to care for patient's symptoms after the underlying diagnosis was made.

A higher number of different drugs was associated with reduced survival, which most likely indicates patients with more comorbidities and more advanced disease.

CONCLUSIONS

- Most concomitant prescribed drugs used by patients with CHC have a low potential for interactions with modern DAAs.
- Simvastatin and carbamazepine were the two most frequently prescribed drugs classified as "*do not co-administer*".
- Prescribed drug use is reduced after CHC diagnosis.
- A lower number of prescribed drugs the year after CHC diagnosis is associated with improved survival.

abbvie