Concomitant use of direct-acting antivirals (DAA) and central nervous system drugs in patients with hepatitis C virus infection

Uso concomitante de antivirales de acción directa (AAD) y fármacos con acción sobre el sistema nervioso central: Consideraciones en el perfil actual del paciente con hepatitis C

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Abstract

Our objective was to determine potential drug interactions (DI) between pangenotypic direct-acting antivirals (pDAA) and concomitant central nervous system (CNS) medication in patients with chronic hepatitis C virus (HCV). Transversal design. Patients aged ≥ 18 years on treatment with pDAA during 2017 were included. The variables collected were comorbidity, concomitant CNS medication and potential DI. The pDAA analyzed were a) Sofosbuvir/Velpatasvir (SOF/VEL), b) Glecaprevir/Pibrentasvir (GLE/PIB) and c) Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX). Descriptive statistical analysis. We recruited 1,170 patients (mean age 60.1 years, 56.4% male). Mean concomitant drug use was 3.2 per patient/year. The percentages of potential / possible DI between the DAAs and the concomitant drugs on the CNS were: 2.7% contraindications, 11.3% significant and 4.2% weak. By pDAA, the percentages were: SOF/VEL (2.7%; 0.0%; 4.4%), GLE/GDP (2.7%; 26.5%; 1.6%) SOF/VEL/VOX (2.7%; 6.8%; 4.4%), respectively. Concomitant CNS medication was used in one third of HCV patients. It is important to select a pDAA with a low rate of potential DI to simplify treatment. SOF/VEL is a good alternative compared with the other pDAA studied, mainly due to the concomitant use of antipsychotics and analgesics.

Keywords: HCV; central nervous system; drug interactions; pangenotypic direct-acting antivirals.

Resumen

El objetivo fue determinar las potenciales interacciones farmacológicas (IF) entre los antivirales de acción-directa pangenotípicos (AADp) y la medicación-concomitante sobre el sistema nervioso central (SNC) asociada a los pacientes portadores del virus de la hepatitis C crónica (VHC). Se realizó un diseño transversal. Se incluyeron pacientes ≥18 años en tratamiento con AADp durante el año 2017. Las variables recogidas fueron: comorbilidad, medicación-concomitante (SNC) y potenciales IF. Los AADp analizados fueron: a) Sofosbuvir/Velpatasvir (SOF/VEL), b) Glecaprevir/Pibrentasvir (GLE/PIB) y c) Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX). Análisis-estadístico descriptivo. Se reclutaron 1.170 pacientes; edad-media de 60,1 años y el 56,4% varones. El promedio de medicamentos-concomitantes fue de 3,2 por paciente/año. El porcentaje de potenciales/posibles IF entre los AADp y los medicamentos-concomitantes sobre el SNC fueron: 2,7% contraindicaciones, 11,3% significativas y 4,2% débiles. En función de los AADp, estos porcentajes fueron los siguientes: SOF/VEL (2,7%; 0,0%; 4,4%), GLE/PIB (2,7%; 26,5%; 1,6%) y SOF/VEL/VOX (2,7%; 6,8%; 4,4%), respectivamente. Un tercio de los pacientes con VHC muestran un uso de medicación-concomitante de acción sobre el SNC. Será importante seleccionar un AADp que tenga una baja tasa de potenciales IF para simplificar el tratamiento. SOF/VEL se presenta como una buena alternativa en comparación con los AADp seleccionados, principalmente en el uso concomitante de antipsicóticos y analgésicos.

Palabas clave: VHC; sistema nervioso central; interacciones medicamentosas; antivirales de acción directa pangenotípicos.

Chronic hepatitis C virus (HCV) infection is a worldwide health problem, affecting 120-150 million people, with a prevalence of between 0.5-2% of the general population (European Association for the Study of the Liver, 2018; World Health Organization, 2018). New cases of the disease continue to be detected, especially among young people and parenteral drug users. Early detection and treatment are therefore important aspects in the prevention of the disease (European Association for the Study of the Liver, 2018).

In the fight against HCV, new DAA molecules taking advantage of the numerous therapeutic targets offered by the virus replication cycle have revolutionized HCV treatment (Calleja et al., 2018). The serve the purpose of achieving greater efficacy and a reduction of possible side effects (Calleja et al., 2018; Zoratti et al., 2020). Advances in research on the virus' replication mechanisms have allowed potential therapeutic targets to be identified. Three different families of DAAs are available, with clear pharmacokinetic differences: a) NS3/4A protease inhibitors, b) NS5A replication complex inhibitors, and c) NS5B polymerase inhibitors. With these pharmacological groups, it is possible to act on three phases of the HCV replication process (inhibiting: viral protease, NS5A protein and NS5B polymerase). With protease inhibitors, potential drug interactions (DI) should be checked before recommending their use; NS5A protein inhibitors are potent and effective but have a low resistance barrier and variable toxicity profiles, while NS5B polymerase inhibitors have a high genetic barrier and their metabolism generally does not depend on cytochrome P450 (Morozov & Lagaye, 2018). A single DAA cannot by itself prevent the reproduction of HCV (mutations); for this reason, the recommended treatment consists of the use of two/three drugs from different families of inhibitors (Laursen, Sandahl, Kazankov, George & Grønbæk, 2020). Current DAAs are pangenotypic (pDAA), that is, they are effective against all HCV genotypes (Paolucci et al., 2019). In addition, they require shorter treatment durations and have a better safety profile, with lower rates of DI (Benet, Bowman, Koleske, Rinaldi & Sodhi, 2019).

Some studies have shown that two-thirds of patients may have potential DIs with DAAs, with figures close to 20% observed in contraindicated drugs (Lauffenburger et al., 2014; Keast, Holderread, Cothran & Skrepnek, 2019). In Spain, high rates of comorbidity and concomitant medication have been reported as being associated with these HCV patients; the most prescribed therapeutic groups with potential DIs were those related to the cardiovascular system (37.5%) and the central nervous system (34.1%; [CNS]) (Sicras Mainar, Navarro Artieda, Hernández & Morillo, 2019).

Comorbidities are common in patients with HCV. These patients may be on multiple medications, a circumstance that can cause adverse effects and/or potential DIs (Calleja et al., 2018). In general, a careful review of the medication patients are taking is advised when prescribing a pDAA. However, little information is available on the risk of presenting a DI when administering a pDAA to these patients (concomitant medication) at the population level, so reporting data is necessary to advance current scientific knowledge. The objective of this study was thus to determine the potential DIs among the DAAs associated with concomitant CNS treatment in patients with HCV infection.

Patients and methods

A cross-sectional study was carried out. Electronic medical records (EMRs) were obtained from the dissociated BIG-PAC database (data source: secondary; owner: Atrys Health; enrolled population: 1.8 million patients). Primary data are from the computerized medical records from seven integrated health areas (primary care centers and hospitals), part of the Spanish public health service, in seven autonomous communities of Spain. Before being exported to BIG-PAC, EMRs undergo rigorous anonymization in the centers/hospitals of origin, in accordance with Organic Law 3/2018, of December 5, regarding the Protection of Personal Data and Guarantee of Digital Rights. Atrys Health does not have access to the primary data sources (Sicras-Mainar et al., 2019).

Patients included in the study were ≥18 years of age with a diagnosis of HCV (ICD-10-CM [B18.2]), seen and treated with pDAAs during 2017, and meeting the following criteria: a) age ≥ 18 years, b) HCV diagnosis at least 12 months prior to the start of the study, c) participation in the chronic prescription program (≥2 prescriptions of any concomitant medication during the study period), and d) guarantee of regular follow-up of these patients (≥ 2 medical visits). Patients who transferred to other centers and/or moved away and/or out of the health area were excluded. Patients' concomitant medication was detailed in the study to calculate the percentage of potential DIs based on the administration of the different DAAs. The result is a theoretical exercise based on a real distribution in practice.

The variables included in the study were demographic as well as the main associated comorbidities (ICD-10-CM). As a summary variable of general comorbidity, we used the Charlson comorbidity index (relating patient comorbidity to long-term mortality) (Charlson, Pompei, Ales & MacKenzie, 1987). Of the 3,430 patients with HCV, only those subjects receiving concomitant chronic medication acting on the CNS were selected for the study (N=1,170). The therapeutic groups were: anticonvulsants, opioid

analgesics, antidepressants, anxiolytics, antipsychotics, sedatives or hypnotics.

Treatment description (concomitant medication, CNS) was obtained in accordance with the Anatomical Therapeutic Chemical Classification System (The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses, 2019). Assigning a pDAA to a patient was based on the criteria of the specialist (prescribing physician). The selected DAAs (most frequently prescribed in Spain) were: a) Sofosbuvir/Velpatasvir (SOF/VEL), b) Glecaprevir/Pibrentasvir (GLE/PIB) and c) Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX). It should be noted that the concomitant medication was analyzed during the antiviral treatment period and only with the chronic or habitual medication administered to the patients. Concomitant medications having potential DIs with action on the CNS are detailed in Figure 1A. To determine the potential effect of possible DIs, the University of Liverpool recommendations were followed (University of Liverpool HIV and Hepatitis Pharmacology Group Drug Interaction Charts, 2020), in collaboration with the European Association for the Study of Hepatic Diseases (European Association for the Study of the Liver, 2018) and HCV treatment guidelines (World Health Organization, 2018). The potential DIs were identified as: a) contraindication, b) significant and c) weak. In addition, the main indications/reasons for prescription were identified for some active ingredients such as quetiapine and oxcarbazepine. Quetiapine was reviewed as it was the most frequently prescribed drug, and oxcarbazepine as it is contraindicated with all three pDAAs analyzed.

Database search criteria were structured using SQL script. Data were carefully reviewed through exploratory analysis and preparation for analysis, observing frequency distributions and checking for possible recording or coding errors. A descriptive statistical analysis was carried out with absolute and relative frequencies for qualitative, and means and standard deviations (SD) for quantitative data. The respective 95% confidence intervals (CI) were calculated.

Results

We identified 1,170 patients (34.1%) with HCV who were receiving concomitant medication acting on the CNS. Mean age was 60.1 years (SD: 10.8), 56.4% were men, and mean Charlson index was 1.0 (SD: 1.1). The following stood out among the comorbidities: arterial hypertension (33.4%), anxiety disorder (31.9%), dyslipidemia (21.6%),

A) By active principle.

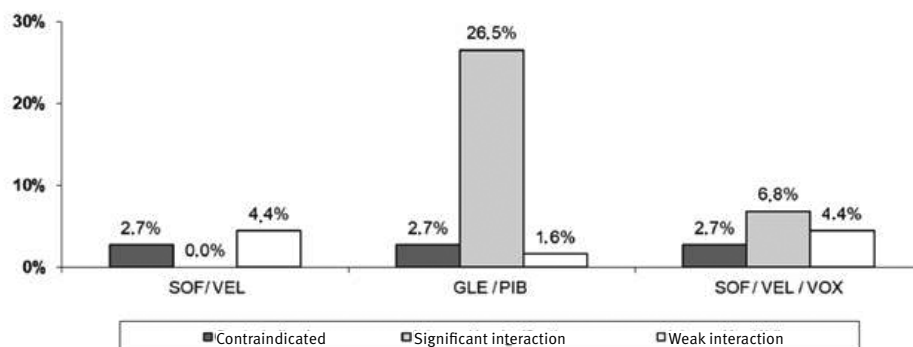| pDAA	N (%)	CNS drug	DI magnitude
SOF/VEL	32 (2.7%)	Oxcarbazepine	Contraindicated
	51 (4.4%)	Buprenorfine	Weak
GLE/PIB	32 (2.7%)	Oxcarbazepine	Contraindicated
	117 (10%)	Quetiapine	Significant
	79 (6.8%)	Fentanyl	
	79 (6.8%)	Paliperidone	
	33 (2.8%)	Aripiprazole	
	26 (2.2%)	Oxycodone	
	19 (1.6%)	Clotiapine	Weak
SOF/VEL/VOX	32 (2.7%)	Oxcarbazepine	Contraindicated
	79 (6.8%)	Paliperidone	Significant
	51 (4.4%)	Buprenorfine	Weak

B) By pDAA.

Figure 1. Potential drug interactions between pDAAs and concomitant drugs of the central nervous system.

Note. pDAA: pangenotypic direct-acting antivirals; CNS: central nervous system; DI: drug interaction; SOF/VEL: sofosbuvir/velpatasvir; GLE /PIB: glecaprevir/pibrentasvir; SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir.

diabetes mellitus (17.4%), addictions (6.7%), liver cirrhosis (5.8%) and AIDS/HIV (1.0%).

The average number of concomitant medications (active ingredients) was: 3.2 (SD: 2.1) per patient/year. The breakdown by CNS therapeutic groups was: a) psycho-anxiolytic (N=744, 64%), b) psychoanalytic-antidepressant (N=679, 58%), c) antiepileptic (N=494, 42%) and d) analgesics (N=429, 37%). Prominent among the active ingredients in these therapeutic groups and showing potential DI with a pDAA were: quetiapine (N=117), fentanyl (N=79), paliperidone (N=79), buprenorphine (N=51), aripiprazole (N=33), oxcarbazepine (N=32), oxycodone (N=26), and clotiapine (N=19) (Figure 1A).

The percentage of potential DIs on the CNS were: 2.7% (95% CI: 1.8-3.6%) contraindications, 11.3% (95% CI: 9.5-13.1%) significant and 4.2% (95% CI: 3.1-5.3%) weak. Based on the DAAs, these percentages [95% CI] were as follows: SOF/VEL (2.7% [1.8-3.6%]; 0.0% [0.0-0.0%]; 4.4% [3.2-5.6%]), GLE / GDP (2.7% [1.8-3.6%]; 26.5% [24.0-29.0%]; 1.6% [0.9-2.3%]) and SOF/VEL/VOX (2.7% [1.8-3.6%]; 6.8% [5.4-8.2%]; 4.4% [3.2-5.6%]), respectively (Figure 1B).

Grounds for prescribing the selected active ingredients were: a) quetiapine (N=117): states of agitation / personality disorder (N=65, 56%), bipolar disorder (N=38, 32%) and schizophrenia (N=14, 12%); and b) oxcarbazepine (N=32): unspecified seizures (N=18, 56%) and epileptic seizures (N=14, 44%).

Discussion

The results of the study show that people with HCV are associated with significant comorbidity and use of medication, leading to greater exposure to potential DIs on receiving antiviral treatment. Although the study was carried out only on concomitant CNS medications, 11.3% had significant DIs and 2.7% were contraindicated. Awareness of DIs represents a challenge for treating HCV infection.

DIs in patients with HCV are common. Maasoumy (2013), for example, investigated the risk of potential DIs in subjects treated with protease inhibitors (telaprevir, boceprevir) in a German hospital and found that half of the patients were exposed to a drug with potential interaction (Maasoumy et al., 2013). Some systematic reviews have shown high rates of potential DIs and their potential interaction mechanisms from a theoretical perspective (Ahmed, Lutchman & Kwo, 2017; Garrison, German, Mogalian & Mathias, 2018; Talavera et al., 2017). Langness (2017) determined that hypertensive agents, analgesics, and psychiatric medications cause frequent interactions with DAAs (sofosbuvir/simeprevir, sofosbuvir/ledipasvir, sofosbuvir/ribavirin, paritaprevir/ritonavir/ombitasvir/dasabuvir). The authors conclude that drug interactions are frequent (1.2 per patient), and that DAA treatment may require adjustments to concomitant medications (Langness et al., 2017). Kondili (2017) (study on sofosbuvir/ribavirin, sofosbuvir/simeprevir, sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir/dasabuvir), highlighted that 30-44% of patients undergoing DAA treatment are at risk of significant interactions. The authors underlined the need for greater awareness in the administration of these drugs, especially in patients with moderate/severe liver disease (Kondili et al., 2017). Our results are in line with these contributions, although we observed a lower rate of relevant DIs. This circumstance may be due to the fact that the study was performed on pDAAs (later marketed) and that we only included drugs acting on the CNS.

Furthermore, SOF/VEL presented a lower rate of DI. SOF is an inhibitor of the NS5B polymerase, while VEL is an inhibitor of the NS5A replication complex. GLE is a pangenotypic inhibitor of the HCV NS3/4A protease essential for viral replication. While PIB is a pangenotypic inhibitor of HCV NS5A, concomitant administration of GLE/PIB can increase exposure to certain medications (digoxin, dabigatran, statins, ethinyl estradiol) (Ahdmed et al., 2017; Talavera et al., 2017). The intracellular metabolic activation pathway of SOF is mediated by nucleotide phosphorylation pathways and hydrolases, generally of low affinity and high capacity, so they are unlikely to be affected by concomitant medications (Kondilii et al., 2017). Recent reviews show that drug combinations with SOF generally have fewer interactions than regimens based on protease inhibitors. However, the analysis of each interaction is theoretical and more interaction studies would be needed to confirm their real effects (Roncero, Villegas, Martínez-Rebollar & Buti, 2018). It appears that the key to interpreting DIs is based on knowledge of the pharmacokinetic profiles of drugs and their ability to inhibit CYP450-3A4 and transporters (hepatic, intestinal) in relation to their potential clinical consequences (Talavera et al., 2017). It should be noted that there may be some discrepancies between the licensed indications for a drug and its actual therapeutic use.

On a practical level, it should be noted that the potential DIs of contraindicated medication and significant interactions are the most clinically relevant and, therefore, those requiring greater vigilance (European Association for the Study of the Liver, 2018). Thus, given the short period of DAA administration, some concomitant medications could be substituted or the administered dose reduced when introducing DAAs. In other cases, for example patients coinfected with HIV/HCV, perhaps another kind of intervention would be preferable, such as selecting the DAA type more carefully. Additionally, it will always be necessary to ask the patient about the use of other drugs, such as those paid for privately (homeopathic,

supplements, vitamins, etc.) or those bought without a prescription.

The article shows the limitations inherent in cross-sectional/retrospective studies, such as underreporting of the disease, or the possible variability among professionals and patients. As a cross-sectional study, it did not take possible confounding factors into account, so the results of the study should be interpreted with caution. Furthermore, the study did not quantify the degree of liver fibrosis (liver damage) in patients at baseline; in our opinion, however, this circumstance should already have been taken into account by the specialist prior to prescribing the pDAA. The efficacy and safety of the concomitant medication associated with certain chronic diseases (indication and prescription in dementia, psychosis, etc.) were also not taken into consideration, which may have an impact on the manifestation of DI. It would have been relevant to know the specialist doctor's criteria for prescribing a DAA, possible drug addictions and/or the indicated doses of drugs with action on the CNS, to mention a few examples, since these are circumstances that can cause real DIs in patients (Roncero et al., 2018).

Potential interactions can pose problems in clinical practice, although many could be avoided by adjusting the pharmacological dose or selecting a safer alternative, provided sufficient knowledge and experience are available to handle these pharmacokinetic issues (Keast et al., 2019). In conclusion, a third of patients with HCV show concomitant use of medication with action on the CNS. It is important to select a pDAA with a low rate of potential DIs to simplify treatment. SOF/VEL is shown to be a good alternative to the selected pDAAs.

Conflict of interests

Author contributions

Conception and design of the manuscript by A. Sicras. Data collection and statistical analysis by A. Sicras. All authors contributed to data interpretation, drafting, revision and approval of the submitted manuscript.

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References

Ahmed, A., Lutchman, G. A. & Kwo, P. Y. (2017). Drug-drug interactions in hepatitis C virus treatment: Do they really matter? *Clinical Liver Disease, 10,* 111-115. doi:10.1002/cld.668.

Benet, L. Z., Bowman, C. M., Koleske, M. L., Rinaldi, C. L. & Sodhi, J. K. (2019). Understanding drug-drug interaction and pharmacogenomic changes in pharmacokinetics for metabolized drugs. *Journal of Pharmacokinetics and Pharmacodynamics, 46,* 155-163. doi:10.1007/s10928-019-09626-7.

Calleja, J. L., Macias, J., Forns, X., Garcia, F., Berenguer, M., Garcia Deltoro, M.,… Pineda, J. A. (2018). Guidelines on treatment of hepatitis C virus infection. Spanish Association for the Study of the Liver (AEEH). Guía de tratamiento de la infección por virus de la hepatitis C. Asociación Española para el Estudio del Hígado (AEEH). *Gastroenterologia y Hepatologia, 41,* 597-608. doi:10.1016/j.gastrohep.2018.07.010.

Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Dseases, 40,* 373-383. doi:10.1016/0021-9681(87)90171-8.

European Association for the Study of the Liver (2018). EASL Recommendations on Treatment of Hepatitis C 2018. *Journal of Hepatology, 69,* 461-511. doi:10.1016/j.jhep.2018.03.026.

Garrison, K. L., German, P., Mogalian, E. & Mathias, A. (2018). The drug-drug interaction potential of antiviral agents for the treatment of chronic hepatitis C infection. *Drug Metabolism and Disposition: The Biological Fate of Chemicals, 46,* 1212-1225. doi:10.1124/dmd.117.079038.

Keast, S. L., Holderread, B., Cothran, T. & Skrepnek, G. H. (2019). Hepatitis C direct-acting antiviral treatment selection, treatment failure, and use of drug-drug interactions in a state medicaid program. *Journal of Managed Care and Specialty Pharmacy, 25,* 1261-1267. doi:10.18553/jmcp.2019.25.11.1261.

Kondili, L. A., Gaeta, G. B., Leluzzi, D., Zignego, A. L., Monti, M., Gori, A.,… Puoti, M. (2017). Real-life data on potential drug-drug interactions in patients with chronic hepatitis C viral infection undergoing antiviral therapy with interferon-free DAAs in the PITER Cohort Study. *PloS One, 12,* e0172159. doi:10.1371/journal.pone.0172159.

Langness, J. A., Nguyen, M., Wieland, A., Everson, G. T. & Kiser, J. J. (2017). Optimizing hepatitis C virus treatment through pharmacist interventions: Identification and management of drug-drug interactions. *World Journal of Gastroenterology, 23,* 1618-1626. doi:10.3748/wjg.v23.i9.1618.

Lauffenburger, J. C., Mayer, C. L., Hawke, R. L., Brouwer, K. L., Fried, M. W. & Farley, J. F. (2014). Medication

use and medical comorbidity in patients with chronic hepatitis C from a US commercial claims database: High utilization of drugs with interaction potential. *European Journal of Gastroenterology and Hepatology, 26*, 1073-1082. doi:10.1097/MEG.0000000000000152.

Laursen, T. L., Sandahl, T. D., Kazankov, K., George, J. & Grønbæk, H. (2020). Liver-related effects of chronic hepatitis C antiviral treatment. *World Journal of Gastroenterology, 26*, 2931-2947. doi:10.3748/wjg.v26.i22.2931.

Maasoumy, B., Port, K., Calle Serrano, B., Markova, A. A., Sollik, L., Manns, M. P.,… Wedemeyer, H. (2013). The clinical significance of drug-drug interactions in the era of direct-acting anti-viral agents against chronic hepatitis C. *Alimentary Pharmacology and Therapeutics, 38,* 1365-1372. doi:10.1111/apt.12523.

Morozov, V. A. & Lagaye, S. (2018). Hepatitis C virus: Morphogenesis, infection and therapy. *World Journal of Hepatology, 10*, 186–212. doi:10.4254/wjh.v10.i2.186.

Paolucci, S., Novazzi, F., Piralla, A., Maserati, R., Gulminetti, R., Novati, S.,… Baldanti, F. (2019). Viral dynamics among HCV infected patients with different genotypes treated with genotypic specific or pan-genotypic direct-acting antiviral agent combinations. *Infection and Drug Resistance, 12*, 1975–1984. doi:10.2147/IDR.S205282.

Roncero, C., Villegas, J. L., Martínez-Rebollar, M. & Buti, M. (2018). The pharmacological interactions between direct-acting antivirals for the treatment of chronic hepatitis c and psychotropic drugs. *Expert Review of Clinical Pharmacology, 11*, 999-1030. doi:10.1080/17512433.2018.1519392.

Sicras Mainar, A., Navarro Artieda, R., Hernández, I. & Morillo, R. (2019). Prevalence of the potential drug-drug interactions between pangenotypic direct-acting antivirals and the concomitant medications associated with patients with chronic hepatitis C virus infection in Spain. *Gastroenterologia y Hepatologia, 42*, 465-475. doi:10.1016/j. gastrohep.2019.03.014.

Sicras-Mainar, A., Enríquez, J.L., Hernández, I., Sicras-Navarro, A., Aymerich, T. & Leon, M. (2019). Validation and representativeness of the Spanish BIG-PAC database: Integrated computerized medical records for research into epidemiology, medicines and health resource use (real word evidence). *Value in Health, 22 (Suppl. 3),* S734. doi:10.1016/j.jval.2019.09.1764.

Talavera Pons, S., Boyer, A., Lamblin, G., Chennell, P., Châtenet, F. T., Nicolas, C.,… Abergel, A. (2017). Managing drug-drug interactions with new direct-acting antiviral agents in chronic hepatitis C. *British Journal of Clinical Pharmacology, 83*, 269-293. doi:10.1111/bcp.13095.

The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD): World Health Organization (2019). Retrieved at http://www.who.int-/classifications /atcddd/en/.

University of Liverpool HIV and Hepatitis Pharmacology Group Drug Interaction Charts (2020). Retrieved at http://www.hep-druginteractions.org/Interactions.aspx.

World Health Organization (2018). Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Retrieved at http://www.who.int-/hepatitis/publications/hepatitis-c-guidelines-2018/en/.

Zoratti, M. J., Siddiqua, A., Morassut, R. E., Zeraatkar, D., Chou, R., van Holten, J.,… Druyts, E. (2020). Pangenotypic direct acting antivirals for the treatment of chronic hepatitis C virus infection: A systematic literature review and meta-analysis. *EClinicalMedicine, 18,* 100237. doi:10.1016/j.eclinm.2019.12.007.