Late HCC onset after DAAs therapy in patients with SVR: a type D ADR that requires a longer follow-up?

The new antivirals for the treatment of hepatitis C virus (HCV) are characterised by short duration with an increased sustained virological response (SVR), a reduced follow-up with a significant impact on HCV natural history and health public burden. However they still lack substantial data on long-term disease evolution in real life.[1] More recently Yin et al showed that real-life SVR was similar to clinical study with a reduction in health costs.[2] However, despite the noteworthy results on the virus, the long-term outcome, possible related adverse drug reaction (ADR) and their impact on healthcare cost are still controversial, even when achieving SVR[3] particularly in regards to hepatocellular carcinoma (HCC). At the beginning of 2015, we started to assess the presence of any kind of ADR of these new DAAs on patients suffering chronic HCV infection in the Campania Region where this virus is largely diffused. This kind of approach has been managed throughout the creation of a network involving clinicians and pharmacists to improve the follow-up of the patients under treatment in terms of real-life efficacy and safety. Previously we published data on early ADR[4], however we have continued to follow up these patients throughout the pharmacist-clinician network for at least 36 months. In this regard, here we present our preliminary data on 250 patients who completed at least 66 weeks' follow-up, based on clinical, laboratory, pharmacological and expert ultrasonography every 3 months in our out-patients' clinic. This is part of a large study enrolling 1022 consecutive HCV patients treated with IFN-free DAAs regimens in a group of hospitals and academic centres in southern Italy (Campania Region). Our preliminary findings showed an SVR in 241 out of 250 (97%) patients of which six had a late occurrence of HCC (2.3%)[4] (Table 1). Specifically HCC developed in mean 18.5 months after the end of treatment as one or more nodules (2–3 cm in mean) with thrombosis of the right portal vein and an increase in alpha-fetoprotein 5 x u.n.v (n.v. <15 UI/mL) at time of diagnosis. Further, all patients with de novo HCC had F4 fibrosis at fibroscan evaluation at the time of treatment enrolment. Interestingly all HCC cases

Table 1 Descriptive analysis of our cohort according to those with or without HCC. All patients were evaluated in out-patients' medical clinics every 3 months, with 12 visits every week

	HCC on 241 SVR patients	
Parameter	**Yes (n=6)**	**No (n=235)**
Age (yrs), median (IQR)	66 (60–69)	65 (60.5–71)
Sex, n		
Male	6	198
Female	3	37
BMI, median (IQR)	24 (24–27)	26 (24–28)
Smoke, n	4	100
Potus, n	1	46
Liver stiffness (kPa),	34.6 (22–45)	31.3 (18–39.1)
Treatment regimen*		
SOF + RBV	1	25
SOF + LDV	5	110
SOF + SIM	0	25
SOF + DAK	0	20
2D/3D	0	55
Treatment duration		
12 weeks	5	213
24 weeks	4	116
Genotype, (n)		
1	4	134
2	1	82
3	1	20
4	0	1
Child Pugh Score, n		
A	9	180
B	0	55
HBsAg positivity	0	6
Portal vein thrombosis	2/6	0
OLTx	0/6	0
TACE	3/6	0
Exitus	2/6	0

DAK, daklinza; 3D/2D, paritaprevir/ritonavir/ombitasvir (Viekirax) + Dasabuvir (Exviera); HBsAg, hepatitis B virus surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LDV, ledipasvir; OLTx, orthotopic liver transplant; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virological response; TACE, transarterial chemoembolization.

(six patients) were among those treated with an SOF-based antiviral regimen while no HCC occurred in those not achieving SVR (nine patients) despite F4. Two out of six patients died during follow-up after transarterial chemoembolisation (TACE) treatment for HCC, while one patient died without any possibility of performing any treatment. Finally, of the last three patients, one underwent sorafenib treatment while two are currently under follow-up after TACE. Of note, three out of six of these drug reactions have been included in the Italian spontaneous reporting system (RNF) database in the Campania Region, while the remaining are due to be inserted, being under clinical follow-up. In conclusion, DAAs, despite their efficacy in terms of sustained viral clearance, may need a more careful follow-up by clinicians and pharmacists concerning the occurrence of HCC, in terms of ADR being potentially classified as a type D reaction.[5] This evidence will probably result in an increase in health costs, not only due to the longer clinical observation but also for the HCC-specific treatment, notwithstanding the already high cost of these drugs.

Antonella Nappi,[1] Alessandro Perrella,[2] Luca Rinaldi,[3] Antonio Izzi,[4] Rodolfo Punzi,[4] Luigi Elio Adinolfi,[3] Costanza Sbeglia,[2] Pasquale Bellopede,[2] Adelaide Maddaloni,[2] Nunzia Papa,[1] Micaela Spatarella[1]

[1]HospitalPharmacy - Pharmacovigilance Unit, Ospedali dei Colli, P.O. D.Cotugno, Naples, Italy
[2]VII Unit InfectiousDiseaseand Immunology, Ospedali dei Colli P.O. D.Cotugno, Naples, Italy
[3]Gastroenterology Unit, Università degli Studi della Campania "LuigiVanvitelli", Naples, italy
[4]AORN Ospedali dei Colli, Napoli, Italy

Correspondence to Dr Antonella Nappi, AORN Ospedali dei Colli, P.O. D.Cotugno, Via Quagliariello 54, Naples, Italy; antonella.nappi@ospedalideicolli.itDr Alessandro Perrella; alessandro.perrella@ospedalideicolli.it

Contributors AN, NP and MS were involved in ADR reporting and pharmacovigilance follow-up of the patients. AP, AN and LR were involved in study design and writing and reviewing the paper. AP, LR CS, RP, PB, AI and AM were engaged in patients' follow-up and enrolment.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Nappi A, Perrella A, Rinaldi L, *et al*. *Eur J Hosp Pharm Sci Pract* 2019;**26**:243–244.

Published Online First 14 June 2019

Eur J Hosp Pharm Sci Pract 2019;**26**:243–244. doi:10.1136/ejhpharm-2019-001975

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