European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2020; 24: 983-987

Editorial – HCC in HCV patients and the direct acting antivirals: is there really a link?

A. MARRONE[1], G. FRANCI[2], A. PERRELLA[3], R. NEVOLA[1], A. CHIANESE[2], L.E. ADINOLFI[1], F.C. SASSO[1], L. RINALDI[1]

[1]Department of Advanced Surgical and Medical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy
[2]Department of Experimental Medicine, University of Campania Luigi Vanvitelli, Naples, Italy
[3]Immunological and Neurological Infectious Diseases Unit, Azienda Ospedaliera dei Colli, Cotugno Hospital, Naples, Italy

The onset of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV) patients who achieved the sustained virological response (SVR) after treatment with direct acting antivirals (DAAs) is still a matter of study and debate.

Currently, most of the literature is still focusing attention on the assessment of epidemiological data as well as the incidence of HCC during follow-up, compared to the annual mean rate in cirrhotic patients[1-9]. Globally, among the results of several studies[3,4,10-13], a trend towards a progressive reduction or stability of HCC risk with SVR seems to be prevalent. Furthermore, scholars[14-17] have shown, especially in the early stages after treatment, the appearance of unexpectedly large HCC lesions. More recently, some preliminary papers are showing a late HCC *de novo* occurrence in patients after more than 18 months of SVR, suggesting possible other mechanisms subtended to HCC occurrence even in absence of HCV chronic inflammation[18]. Therefore, these contrasting epidemiological data clearly suggest that mechanisms in carcinogenesis are still unclear, requiring further investigations. Several papers have identified some variables most frequently associated with the appearance of HCC *de novo*, such as the value of platelets, liver stiffness, portal hypertension, alpha-feto protein value, alcohol consumption, metabolic factors or the most advanced stage of cirrhosis[19-25]. However, these elements appear to be major risk predictors but are not attributable to direct carcinogenic effect. The possible indirect implication of DAAs was immediately discussed.

Our group, in a recent prospective multicenter work[26], has highlighted a predominance of HCC *de novo* in patients who have been treated with sofosbuvir without ribavirin in the 2015-2017 period. Our hypothesis is based on the lack of immunomodulatory protective effect of ribavirin[27] and on the possible damage on the mitochondrial RNA of sofosbuvir[28].

Likewise, some authors focused on the reduced immunosurveillance induced by early and rapid viral clearance, which may partly explain the controversial relationship between eradication and HCC occurrence. Researchers[29,30] have highlighted the possible role of some cytokines as carcinogenesis co-factors. To date, there is no direct evidence of an involvement of DAAs in the carcinogenesis.

However, it should also be considered that we still do not have details on the new antivirals according to their possible immunomodulatory activity. Indeed, in order to infection disease, the antivirals are well known to exert some immunomodulatory activity. The most interesting immunomodulating activity is for two sub-set of antivirals as the protease inhibitors as, for instance, fosamprenavir or darunavir[31,32] and maraviroc[33] being involved in the modulation of the angiogenesis, tumor growth and invasion, inflammation, antigen processing and presentation, cell survival. Instead, concerning HCV antivirals, ribavirin has been demonstrated to exert a kind of immunomodulatory activity markedly reducing macrophage activation and diminishing Th2 cytokine production while preserving Th1 cytokine production and stimulating humoral immune response[34,35]. All these studies and the current literature debate about HCC *de novo* onset after SVR following new DAAs therapy clearly suggest that most of the drugs, even if to be considered safe, may exert some important effect on host that should be considered.

Despite the fact that the DAA therapies are able to remove the HCV from the patients, the epigenetic impact on cells persist also in absence of the virus itself. It is becoming emergent the relationship and

Corresponding Author: Luca Rinaldi, MD; e-mail: lucarinaldi@hotmail.it

connection among these alterations and the risk of development of HCC during the lifetime[36]. The HCV infection determines an epigenetic furrow with a determinate signature. This signature is made of DNA methylation and histone modifications. Hamdane et al[37] highlights how the acetylation of lysine 27 on the histone 3 (H3K27Ac), due to the HCV, promote the alteration of gene expression involved in the Protein Kinase B (AKT), mammalian Target of rapamycin (mTor), Tumor Necrosis Factor alpha (TNF-α) pathways with an increase of HCC risk. Indeed, the overexpression of the SPHK1 gene (mediator of sphingolysin phosphorylation) and SP1 (regulator of inhibition of apoptosis and promotion of proliferation) has been demonstrated to play a crucial role in the TNF-α signalling pathway[37]. HCV infection reflects on DNA methylation alteration. As double side of the same coin, DNA methylation is responsible in gene activation and silencing. HCV infection can determine in the same time hyper and lower-methylated region. Zheng et al[38] highlights how the decrease in specific region, such as the interspersed nuclear element-1 (LINE-1) is a direct consequence of HCV infection. This aspect is due to natural kill cell-dependent innate immune response activation with an aberrant DNA methylation in hepatocytes[39]. All together the information opens the scenario of epigenetic relationship among DAA treated patients and HCC risk.

An additional pathogenetic mechanism can be determined by gut microbiota which has been demonstrated to have an important connection in the inflammation, liver fibrosis, and HCC[40]. Indeed, a recent study showed that HCV eradication with DAAs in patients with cirrhosis is associated with a modification of the gut microbiota, which correlates with fibrosis and inflammation, but does not improve intestinal barrier function[41].

HCC is still today a high mortality oncological illness[42] with multifactorial aspects related to genetics[43,44] to virology[45] and metabolic factors[46,47].

The research for effective medical therapies is subject to an understanding of these mechanisms. The possible indirect role of DAAs in carcinogenesis may represent a further food for thought.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Piñero F, Mendizabal M, Ridruejo E, Herz Wolff F, Ameigeiras B, Anders M, Schinoni MI, Reggiardo V, Palazzo A, Videla M, Alonso C, Santos L, Varón A, Figueroa S, Vistarini C, Adrover R, Fernández N, Perez D, Tanno F, Hernández N, Sixto M, Borzi S, Bruno A, Cocozzella D, Soza A, Descalzi V, Estepo C, Zerega A, de Araujo A, Cheinquer H, Silva M; LALREAN. Treatment with direct-acting antivirals for HCV decreases but does not eliminate the risk of hepatocellular carcinoma. Liver Int 2019; 39: 1033-1043.
2) Mariño Z, Darnell A, Lens S, Sapena V, Díaz A, Belmonte E, Perelló C, Calleja JL, Varela M, Rodriguez M, de Lope CR, Llerena S, Torras X, Gallego A, Sala M, Morillas RM, Minguez B, Llaneras J, Coll S, Carrion JA, Iñarrairaegui M, Sangro B, Vilana R, Sole M, Ayuso C, Ríos J, Forns X, Bruix J, Reig M. Time association between hepatitis C therapy and hepatocellular carcinoma emergence in cirrhosis: relevance of non-characterized nodules. J Hepatol 2019; 70: 874-884.
3) Romano A, Angeli P, Piovesan S, Noventa F, Anastassopoulos G, Chemello L, Cavalletto L, Gambato M, Russo FP, Burra P, Vincenzi V, Scotton PG, Panese S, Tempesta D, Bertin T, Carrara M, Carlotto A, Capra F, Carolo G, Scroccaro G, Alberti A. Newly diagnosed hepatocellular carcinoma in patients with advanced hepatitis C treated with DAAs: a prospective population study. J Hepatol 2018; 69: 345-352.
4) Calvaruso V, Cabibbo G, Cacciola I, Petta S, Madonia S, Bellia A, Tinè F, Distefano M, Licata A, Giannitrapani L, Prestileo T, Mazzola G, Di Rosolini MA, Larocca L, Bertino G, Digiacomo A, Benanti F, Guarneri L, Averna A, Iacobello C, Magro A, Scalisi I, Cartabellotta F, Savalli F, Barbara M, Davì A, Russello M, Scifo G, Squadrito G, Cammà C, Raimondo G, Craxì A, Di Marco V; Rete Sicilia Selezione Terapia-HCV (RESIST-HCV). Incidence of hepatocellular carcinoma in patients with HCV-associated cirrhosis treated with direct acting antiviral agents. Gastroenterology 2018; 155: 411-421.
5) Nagata H, Nakagawa M, Asahina Y, Sato A, Asano Y, Tsunoda T, Miyoshi M, Kaneko S, Otani S, Kawai-Kitahata F, Murakawa M, Nitta S, Itsui Y, Azuma S, Kakinuma S, Nouchi T, Sakai H, Tomita M, Watanabe M; Ochanomizu Liver Conference Study Group. Effect of interferon-based and -free therapy on early occurrence and recurrence of hepatocellular carcinoma in chronic hepatitis C. J Hepatol 2017; 67: 933-939.
6) Nagaoki Y, Imamura M, Aikata H, Daijo K, Teraoka Y, Honda F,Nakamura Y, Hatooka M, Morio R, Morio K, Kan H, Fujino H, Kobayashi T, Masaki K, Ono A, Nakahara T, Kawaoka T, Tsuge M, Hiramatsu A, Kawakami Y, Hayes CN, Mi-

ki D, Ochi H, Chayama K. The risks of hepatocellular carcinoma development after HCV eradication are similar between patients treated with peg-interferon plus ribavirin and direct-acting antiviral therapy. PLoS One 2017; 12: e0182710.

7) Bielen R, Moreno C, Van Vlierberghe H, Bourgeois S, Mulkay JP, Vanwolleghem T, Verlinden W, Brixco C, Decaestecker J, de Galocsy C, Janssens F, Van Overbeke L, Van Steenkiste C, D'Heygere F, Cool M, Wuyckens K, Nevens F, Robaeys G. The risk of early occurrence and recurrence of hepatocellular carcinoma in hepatitis C-infected patients treated with direct-acting antivirals with and without pegylated interferon: a Belgian experience. J Viral Hepat 2017; 24: 976-981.

8) Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2017. pii: S0168-8278(17)32273-0.

9) Li DK, Ren Y, Fierer DS, Rutledge S, Shaikh OS, Lo Re V 3rd, Simon T, Abou-Samra AB, Chung RT, Butt AA. The short-term incidence of hepatocellular carcinoma is not increased after hepatitis C treatment with direct-acting antivirals: an ERCHIVES study. Hepatology 2018; 67: 2244-2253.

10) Cheung MCM, Walker AJ, Hudson BE, Verma S, Mc Lauchlan J, Mutimer DJ, Brown A, Gelson WTH, MacDonald DC, Agarwal K, Foster GR, Irving WL; HCV Research UK. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016; 65: 741-747.

11) Foster GR, Irving WL, Cheung MC, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ, Brown A, Gelson WT, MacDonald DC, Agarwal K; HCV Research, UK. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016; 64: 1224-1231.

12) Kobayashi M, Suzuki F, Fujiyama S, Kawamura Y, Sezaki H, Hosaka T, Akuta N, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kumada H. Sustained virologic response by direct antiviral agents reduces the incidence of hepatocellular carcinoma in patients with HCV infection. J Med Virol 2017; 89: 476-483.

13) Carrat F, Fontaine H, Dorival C, Simony M, Diallo A, Hezode C, De Ledinghen V, Larrey D, Haour G, Bronowicki JP, Zoulim F, Asselah T, Marcellin P, Thabut D, Leroy V, Tran A, Habersetzer F, Samuel D, Guyader D, Chazouilleres O, Mathurin P, Metivier S, Alric L, Riachi G, Gournay J, Abergel A, Cales P, Ganne N, Loustaud-Ratti V, D'Alteroche L, Causse X, Geist C, Minello A, Rosa I, Gelu-Simeon M, Portal I, Raffi F, Bourliere M, Pol S; French ANRS CO22 Hepather cohort. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet 2019; 393: 1453-1464.

14) Rinaldi L, Di Francia R, Coppola N, Guerrera B, Imparato M, Monari C, Nevola R, Rosato V, Fontanella L, Franci G, Porta G, Messina V, Ascione A, Adinolfi LE. Hepatocellular carcinoma in HCV cirrhosis after viral clearance with direct acting antiviral therapy: preliminary evidence and possible meanings. WCRJ 2016; 3: e748.

15) Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, Foschi FG, Lenzi M, Mazzella G, Verucchi G, Andreone P, Brillanti S. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct acting antivirals. J Hepatol 2016; 65: 727-733.

16) Kozbial K, Moser S, Schwarzer R, Laferl H, Al-Zoairy R, Stauber R, Stättermayer AF, Beinhardt S, Graziadei I, Freissmuth C, Maieron A, Gschwantler M, Strasser M, Peck-Radosalvjevic M, Trauner M, Hofer H, Ferenci P. Unexpected high incidence of hepatocellular carcinoma in cirrhotic patients with sustained virologic response following interferon-free direct-acting antiviral treatment. J Hepatol 2016; 65: 856-858.

17) Cardoso H, Vale AM, Rodrigues S, Gonçalves R, Albuquerque A, Pereira P, Lopes S, Silva M, Andrade P, Morais R, Coelho R, Macedo G. High incidence of hepatocellular carcinoma following successful interferon-free antiviral therapy for hepatitis C associated cirrhosis. J Hepatol 2016; 65: 1070-1071.

18) Perrella A, Izzi A, Punzi R, Adinolfi E, Sbreglia C, Bellopede P, Galeota Lanza A, Martucci F, Rinaldi L. Late HCC onset after direct antiviral agents therapy in patients with sustained virological response: do we need to reconsider their efficacy according to long term follow-up? Scand J Gastroenterol 2018; 53: 1025-1026.

19) Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 2017; 153: 996-1005.

20) Finkelmeier F, Dultz G, Peiffer KH, Kronenberger B, Krauss F, Zeuzem S, Sarrazin C, Vermehren J, Waidmann O. Risk of de novo hepatocellular carcinoma after HCV treatment with direct-acting antivirals. Liver Cancer 2018; 7: 190-204.

21) Van der Meer AJ, Feld JJ, Hofer H, Almasio PL, Calvaruso V, Fernández-Rodríguez CM, Aleman S, Ganne-Carrié N, D'Ambrosio R, Pol S, Trapero-Marugan M, Maan R, Moreno-Otero R, Mallet V, Hultcrantz R, Weiland O, Rutter K, Di Marco V, Alonso S, Bruno S, Colombo M, de Knegt RJ, Veldt BJ, Hansen BE, Janssen HLA. Risk of cirrhosis-related complications in patients with advanced fibrosis following hepatitis C virus eradication. J Hepatol 2017; 66: 485-493.

22) Lleo A, Aglitti A, Aghemo A, Maisonneuve P, Bruno S, Persico M; Collaborators. Predictors of hepatocellular carcinoma in HCV cirrhotic patients treated with direct acting antivirals. Dig Liver Dis 2019; 51: 310-317.

23) Ooka Y, Miho K, Shuntaro O, Nakamura M, Ogasawara S, Suzuki E, Yasui S, Chiba T, Arai M, Kanda T, Maruyama H, Yokosuka O, Kato N, Mochizuki H, Omata M. Prediction of the very early occurrence of HCC right after DAAs therapy for HCV infection. Hepatol Int 2018; 12: 523-530.

24) Rinaldi L, Guarino M, Perrella A, Pafundi PC, Valente G, Fontanella L, Nevola R, Guerrera B, Iuliano N, Imparato M, Trabucco A, Sasso FC, Morisco F, Ascione A, Piai G, Adinolfi LE. Role of liver stiffness measurement in pre-

dicting HCC occurrence in direct-acting antivirals setting: a real-life experience. Dig Dis Sci 2019; 64: 3013-3019.

25) Iuliano N, Pafundi PC, Acierno C, Monaco L, Fascione MC, Mastrocinque D, Marotta G, Nevola R, Marrone A, Sasso FC, Adinolfi LE, Rinaldi L. Impact of type 2 diabetes on HCC appearance in patients treated with direct acting antivirals. WCRJ 2018; 5: e1048.

26) Rinaldi L, Perrella A, Guarino M, De Luca M, Piai G, Coppola N, Pafundi PC, Ciardiello F, Fasano M, Martinelli E, Valente G, Nevola R, Monari C, Miglioresi L, Guerrera B, Berretta M, Sasso FC, Morisco F, Izzi A, Adinolfi LE. Incidence and risk factors of early HCC occurrence in HCV patients treated with direct acting antivirals: a prospective multicentre study. J Transl Med 2019; 17: 292.

27) Kobayashi T, Nakatsuka K, Shimizu M, Tamura H, Shinya E, Atsukawa M, Harimoto H, Takahashi H, Sakamoto C. Ribavirin modulates the conversion of human CD4(+) CD25(–) T cell to CD4(+) CD25(+) FOXP3(+) T cell via suppressing interleukin-10-producing regulatory T cell. Immunology 2012; 137: 259-270.

28) Fenaux M, Lin X, Yokokawa F, Sweeney Z, Saunders O, Xie L, Lim SP, Uteng M, Uehara K, Warne R, Gang W, Jones C, Yendluri S, Gu H, Mansfield K, Boisclair J, Heimbach T, Catoire A, Bracken K, Weaver M, Moser H, Zhong W. Antiviral nucleotide incorporation by recombinant human mitochondrial RNA polymerase is predictive of increased in vivo mitochondrial toxicity risk. Antimicrob Agents Chemother 2016; 60: 7077-7085.

29) Debes JD, van Tilborg M, Groothuismink ZMA, Hansen BE, Schulze Zur Wiesch J, von Felden J, de Knegt RJ, Boonstra A. Levels of cytokines in serum associate with development of hepatocellular carcinoma in patients with HCV infection treated with direct-acting antivirals. Gastroenterology 2018; 154: 515-517.

30) Faillaci F, Marzi L, Critelli R, Milosa F, Schepis F, Turola E, Andreani S, Vandelli G, Bernabucci V, Lei B, D'Ambrosio F, Bristot L, Cavalletto L, Chemello L, Sighinolfi P, Manni P, Maiorana A, Caporali C, Bianchini M, Marsico M, Turco L, de Maria N, Del Buono M, Todesca P, di Lena L, Romagnoli D, Magistri P, di Benedetto F, Bruno S, Taliani G, Giannelli G, Martinez-Chantar ML, Villa E. Liver angiopoietin-2 is a key predictor of de novo or recurrent hepatocellular cancer after HCV direct-acting antivirals. Hepatology 2018; 68: 1010-1024.

31) Perrella A, Sbreglia C, D'Antonio A, Atripaldi L, Perrella O. Fosamprenavir treatment in a highly active antiretroviral therapy schedule induces a HCV-RNA decrease and a Th1 network boost in HIV/HCV-coinfected patients. Clin Microbiol Infect 2010; 16: 676-678.

32) Ermocida A, Mengoni F, Sauzullo I, Rossi R, Ajassa C, Lichtner M, Mastroianni CM, Vullo V. Extravirologic modulation of immune response by an NRTI-sparing antiretroviral regimen including darunavir and maraviroc. New Microbiol 2014; 37: 225-229.

33) Giardino Torchia ML, Ciaglia E Masci AM, Vitiello L, Fogli M, la Sala A, Mavilio D, Racioppi L. Dendritic cells/natural killer cross-talk: a novel target for human immunodeficiency virus type-1 protease inhibitors. PLoS One 5: e11052.

34) Kobayashi T, Nakatsuka K, Shimizu M, Tamura H, Shinya E, Atsukawa M, HarimotoH, Takahashi H, Sakamoto C. Ribavirin modulates the conversion of human CD4(+)CD25(-) T cell to CD4(+) CD25(+) FOXP3(+) T cell via suppressinginterleukin-10-producing regulatory T cell. Immunology 2012; 137: 259-270.

35) Nakatsuka K, Atsukawa M, Shimizu M, Takahashi H, Kawamoto C. Ribavirin contributes to eradicate hepatitis C virus through polarization of T helper 1/2 cell balance into T helper 1 dominance. World J Hepatol 2015; 7: 2590-2596.

36) Perez S, Kaspi A, Domovitz T, Davidovich A, Lavi-Itzkovitz A, Meirson T, Alison Holmes J, Dai CY, Huang CF, Chung RT, Nimer A, El-Osta A, Yaari G, Stemmer SM, Yu ML, Haviv I, Gal-Tanamy M. Hepatitis C virus leaves an epigenetic signature post cure of infection by direct-acting antivirals. PLoS Genet 2019; 15: e1008181.

37) Hamdane N, Jühling F, Crouchet E, El Saghire H, Thumann C, Oudot MA, Bandiera S, Saviano A, Ponsolles C, Roca Suarez AA, Li S, Fujiwara N, Ono A, Davidson I, Bardeesy N, Schmidl C, Bock C, Schuster C, Lupberger J, Habersetzer F, Doffoël M, Piardi T, Sommacale D, Imamura M, Uchida T, Ohdan H, Aikata H, Chayama K, Boldanova T, Pessaux P, Fuchs BC, Hoshida Y, Zeisel MB, Duong FHT, Baumert TF. HCV-induced epigenetic changes associated with liver cancer risk persist after sustained virologic response. Gastroenterology 2019; 156: 2313-2329.

38) Zheng Y, Hlady RA, Joyce BT, Robertson KD, He C, Nannini DR, Kibbe WA, Achenbach CJ, Murphy RL, Roberts LR, Hou L. DNA methylation of individual repetitive elements in hepatitis C virus infection-induced hepatocellular carcinoma. Clin Epigenetics 2019; 11: 145.

39) Okamoto Y, Shinjo K, Shimizu Y, Sano T, Yamao K, Gao W, Fujii M, Osada H, Sekido Y, Murakami S, Tanaka Y, Joh T, Sato S, Takahashi S, Wakita T, Zhu J, Issa JP, Kondo Y. Hepatitis virus infection affects DNA methylation in mice with humanized livers. Gastroenterology 2014; 146: 562-572.

40) Ponziani FR, Nicoletti A, Gasbarrini A, Pompili M. Diagnostic and therapeutic potential of the gut microbiota in patients with early hepatocellular carcinoma. Ther Adv Med Oncol 2019; 11: 1758835919848184.

41) Ponziani FR, Putignani L, Paroni Sterbini F, Petito V, Picca A, Del Chierico F, Reddel S, Calvani R, Marzetti E, Sanguinetti M, Gasbarrini A, Pompili M. Influence of hepatitis C virus eradication with direct-acting antivirals on the gut microbiota in patients with cirrhosis. Aliment Pharmacol Ther 2018; 48: 1301-1311.

42) Ascione A, Fontanella L, Imparato M, Rinaldi L, De Luca M. Mortality from cirrhosis and hepatocellular carcinoma in Western Europe over the last 40 years. Liver Int 2017; 37: 1193-1201.

43) Berretta M, Fisichella R, Spartà D, Lieshi A, Nasti G. Primary liver cancer: clinical aspects, prognostic factors and predictive response to therapy. WCRJ 2015; 2: e561.

44) Canzonieri V, Alessandrini L, Caggiari L, Perin T, Berretta M, Cannizzaro R, De Re V. Hepatocellular carcinoma: an overview of clinico-pathological and molecular perspectives. WCRJ 2015; 2: e485.

45) Marrone A, Capoluongo N, D'Amore C, Pisaturo M, Esposito M, Guastafierro S, Siniscalchi I, Macera M, Boemio A, Onorato L, Rinaldi L, Minichini C, Adinolfi LE, Sagnelli E, Mastrullo L, Coppola N. Eighteen-month lamivudine prophylaxis on preventing occult hepatitis B virus infection reactivation in patients with haematological malignancies receiving immunosuppression therapy. J Viral Hepat 2018; 25: 198-204.

46) Coppola N, De Pascalis S, Messina V, Di Caprio G, Martini S, de Stefano G, Starace M, Stornaiuolo G, Stanzione M, Ascione T, Minichini C, Sangiovanni V, Zampino R, Calò F, Rinaldi L, Persico M, Federico A, Buonomo AR, Borgia G, Gaeta GB, Filippini P, Gentile I. ITPase activity modulates the severity of anaemia in HCV-related cirrhosis treated with ribavirin-containing interferon-free regimens. Antivir Ther 2017; 22: 551-558.

47) Nevola R, Acierno C, Sasso FC, Marrone A, Buffardi F, Adinolfi LE, Rinaldi L. Hepatocellular carcinoma and non-alcoholic fatty liver disease: a dangerous liaison. WCRJ 2019; 6: e1299.