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LETTER TO THE EDITOR

# Interferon free antiviral treatment of chronic hepatitis C in patients affected by β-thalassemia major

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Dear Editor,

Chronic hepatitis C (CHC) significantly affects the prognosis of liver disease [1] and health related quality of life (HRQOL) in patients with β-thalassemia major [2, 3]. CHC cure is a crucial event in the prognosis of the disease, since prevents fibrosis progression, decreases the risk of hepatocellular carcinoma (HCC), and improves survival. Standard antiviral therapy with Pegylated Interferon (PEG-IFN) and Ribavirin (RBV) has long been the standard of care, despite its limited efficacy and increased ribavirin induced hematological adverse events in thalassemic patients [4]. Recently, several novel highly effective direct antiviral agents (DAAs) have been approved for HCV treatment, with impressive cure rates, higher than 90%, after 8–12 weeks of therapy and mild adverse events [5], but there are no published reports documenting the efficacy, safety and impact on QOL of available interferon-free antiviral regimens in patients with β-thalassemia major.

We describe four cases of young patients with β-thalassemia major and advanced fibrosis treated with DAAs for CHC (Table 1). HCV genotype was 1b in all patients except one, which had genotype 4. Cryoglobulins were positive in two patients (cryocrit 1.6 and 3.2%) with no organ involvement. All patients were previously non-responders to PEG-IFN ± RBV treatment. Iron chelation drugs included subcutaneous desferrioxamine and/or oral deferasirox. Antiviral therapy with sofosbuvir (SOF) and ledipasvir (LDV) was started for 12 weeks. All patients achieved sustained virologic response (SVR). Treatment was safe and well tolerated, kidney function remained stable, and the only adverse events were mild asthenia and headache. Iron chelation concomitant medications remained unmodified during treatment, as well as the frequency of blood transfusions. Ferritin levels decreased during therapy in three patients, but in two of them returned to baseline levels at FU3. A reduction of liver stiffness, assessed by transient elastography, occurred from baseline to FU3 in all subjects. All SF36 scales related to mental health and to physical health significantly improved at FU6 compared to baseline (Table 2).

The present case series suggests that 12-week-combination therapy of SOF/LDV is effective and safe in transfusion-dependent β-thalassemia patients with advanced liver fibrosis. Remarkably, no impact of SOF on kidney function was observed as e-GFR values remained stable during therapy and FU.

To our knowledge, no data exist on the interactions between DAAs and iron chelation drugs. We employed SOF and LDV in these patients because this drug combination is associated with limited interactions [6]. Remarkably, in none of the cases, it was necessary to modify iron chelation therapy, and no changes in transfusion requests occurred. Moreover, serum ferritin values, an indirect marker of iron chelation efficacy, showed an improvement during antiviral therapy in all patients but one who reported poor compliance to iron chelation therapy during DAA treatment.

A marked improvement of liver stiffness, which correlates with fibrosis stage assessed by liver biopsy [7], was observed in all patients. This result may be partly due to a reduction and control of liver inflammation [8]; however, an initial regression of liver fibrosis might also have occurred, which is an

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**Table 1** Biochemical and virological characteristics of HCV patients with thalassemia major during the study period

| | Parameters | Baseline (T0) | Treatment week 4 (TW4) | End of treatment (EOT) | Follow-up week 12 (FU3) |
|---|---|---|---|---|---|
| Patient 1 Female 42 years | Hemoglobin (12–15 g/dL) | 10.4 | 12.6 | 12.7 | 12.8 |
| | Total bilirubin (0.3–1.2 mg/dL) | 2.6 | 1.32 | 1.64 | 2 |
| | ALT (7–35 U/L) | 97 | 21 | 17 | 10 |
| | e-GFR (mL/min/1.73m$^2$) | 107 | 107 | 107 | 107 |
| | Serum ferritine (15–150 ng/mL) | 184 | 130 | 88 | 166 |
| | HCV-RNA (IU/mL) | 211.100 | Undetectable | Undetectable | Undetectable |
| | Liver stiffness (KPa) | 10.5 | – | – | 7.1 |
| Patient 2 Female 43 years | Hemoglobin (12–15 g/dL) | 10.9 | 11.7 | 10.8 | 11 |
| | Total bilirubin (0.3–1.2 mg/dL) | 1.5 | 1.2 | 1.6 | 1.67 |
| | ALT (7–35 U/L) | 24 | 14 | 11 | 13 |
| | e-GFR (mL/min/1.73m$^2$) | 112 | 112 | 106 | 112 |
| | Serum ferritine (15–150 ng/mL) | 834 | 556 | 626 | 380 |
| | HCV-RNA (IU/mL) | 1.121.181 | Undetectable | Undetectable | Undetectable |
| | Liver stiffness (KPa) | 10 | – | – | 7.3 |
| Patient 3 Male 37 years | Hemoglobin (12–15 g/dL) | 9.7 | 9.9 | 9.4 | 9.6 |
| | Total bilirubin (0.3–1.2 mg/dL) | 2.72 | 2.81 | 2.63 | 2.38 |
| | ALT (7–35 U/L) | 62 | 26 | 24 | 13 |
| | e-GFR (mL/min/1.73m$^2$) | 145 | 128 | 138 | 138 |
| | Serum ferritine (15–150 ng/mL) | 544 | 667 | 346 | 462 |
| | HCV-RNA (IU/mL) | 473.982 | Undetectable | Undetectable | Undetectable |
| | Liver stiffness (KPa) | 10.4 | – | – | 8.1 |
| Patient 4 Male 38 years | Hemoglobin (12–15 g/dL) | 11.5 | 10.9 | 11.1 | 10.7 |
| | Total bilirubin (0.3–1.2 mg/dL) | 2.03 | 1.11 | 1.31 | 1.41 |
| | ALT (7–35 U/L) | 47 | 19 | 35 | 42 |
| | e-GFR (mL/min/1.73m$^2$) | 128 | 128 | 128 | 128 |
| | Serum ferritine (15–150 ng/mL) | 420 | 684 | 621 | 650 |
| | HCV-RNA (IU/mL) | 4.419.000 | Undetectable | Undetectable | Undetectable |
| | Liver stiffness (KPa) | 10 | – | – | 7 |

important outcome in thalassemic patients, given their rapid fibrosis progression.

Both thalassemia major and CHC affect HRQOL [2, 3, 9], but the contribution of CHC to the impaired HRQOL of

**Table 2** Physical and mental health related quality of life (HRQOL) scores in SF-36 scales before and 24 weeks after antiviral treatment of HCV patients with Thalassemia major

| Patient number | Time | Physical functioning | Role-physical | Bodily pain | General health | Vitality | Social functioning | Role-emotional | Mental health |
|---|---|---|---|---|---|---|---|---|---|
| 1 | T0 | 75 | 75 | 64 | 30 | 60 | 50 | 66 | 56 |
| | FU6 | 85 | 100 | 100 | 25 | 85 | 87 | 100 | 68 |
| 2 | T0 | 50 | 50 | 41 | 5 | 30 | 37 | 33 | 40 |
| | FU6 | 85 | 100 | 84 | 56 | 85 | 87 | 100 | 76 |
| 3 | T0 | 90 | 100 | 84 | 10 | 50 | 75 | 100 | 52 |
| | FU6 | 95 | 100 | 100 | 37 | 85 | 100 | 100 | 76 |
| 4 | T0 | 75 | 80 | 72 | 20 | 50 | 55 | 60 | 54 |
| | FU6 | 91 | 94 | 90 | 35 | 83 | 90 | 100 | 70 |

thalassemic patients has never been assessed. In our case series, a striking improvement of physical and mental dimensions of health, assessed by SF-36 questionnaire, occurred in all patients after HCV cure. This finding suggests that HCV infection plays a prominent, though probably underestimated, role on the impairment of HRQOL of thalassemic patients, and that antiviral treatment has the capacity to affect also this important aspect of patient's health.

**Compliance with ethical standards**

**Conflict of interest** Gloria Taliani has received advisory board and speaking fees from AbbVie, BMS, MSD, Roche, Janssen and Gilead. The other authors have nothing to disclose regarding funding or conflict of interest with respect to this manuscript.

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