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RESEARCH ARTICLE

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Treatment of hepatitis C virus infection with direct-acting antiviral drugs is safe and effective in patients with hemoglobinopathies

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Abstract

Progression of liver fibrosis in patients with hemoglobinopathies is strongly related to the severity of iron overload and the presence of chronic hepatitis C virus (HCV) infection. Effective iron chelation therapy and HCV infection eradication may prevent liver complications. The European Association for the Study of the Liver guidelines recommend interferon-free regimens for the treatment of HCV infection in patients with hemoglobinopathies. However, data regarding the use of direct-acting antiviral drugs (DAAs) in this patient population are few. This observational study evaluated the safety and efficacy of therapy with DAAs in an Italian cohort of patients with hemoglobinopathies, chronic HCV infection and advanced liver fibrosis. Between March 2015 and December 2016, 139 patients received DAAs and completed 12 weeks of follow up after the end of treatment for the evaluation of sustained virological response (12SVR). The 12SVR (93.5%) was comparable with that typically observed in cirrhotic patients without hemoglobinopathies. Three patients died during the period of observation of causes unrelated to DAAs. One patient did not achieve a virological response and five (3.6%) relapsed during 12 weeks of follow-up after the end of therapy. In addition, patients showed significant reductions in serum ferritin at 12 weeks to levels similar to those observed in a control group of 39 patients with thalassemia major without HCV infection, who adhered to chelation therapy and had no overt iron overload. In conclusion, the use of DAAs appears to be safe and effective in patients with hemoglobinopathies and advanced liver disease due to HCV.

1 | INTRODUCTION

Many patients with hemoglobinopathies have been infected with hepatitis C virus (HCV) through blood transfusion, mostly before screening of blood donors was introduced in 1992. In the years immediately after the HCV screening test became available, the prevalence of chronic HCV infection among patients with thalassemia ranged from 4% in Turkey to 85% in Italy. Although the prevalence of HCV infection has progressively decreased over the last 20 years, it is still higher than the general population.[1] Genotype 1b infection is the most frequent in Italy. In epidemiological and cohort studies, the proportion of patients with genotype 1b infection often exceeds 50%. Epidemiological data on Italian patients with thalassemia and chronic HCV infection also indicate that the prevalence of genotype 1b infection if more than 60%.[1] HCV infection is associated with the risk of developing cirrhosis, hepatocellular carcinoma and other liver complications, especially if left

untreated.[2–4] Cirrhosis has been reported in up to 32% of patients with thalassemia[5–9]; these patients are at increased risk of death.[10] Presence of chronic HCV infection and the extent of iron overload are strong predictors of liver fibrosis progression.[5,7,11]

Effective chelation therapy and treatment of HCV infection are needed in order to prevent liver complications and improve morbidity and mortality.[1,7,12] Pegylated interferon (peg-IFN) plus ribavirin (RBV) has been the standard of care for the treatment of chronic HCV infection and cirrhosis.[13] Studies of peg-IFN plus RBV have demonstrated sustained virological response (SVR) rates of 25 − 64% in patients with thalassemia and HCV infection.[14–17] However, peg-IFN and RBV are both associated with anemia.[13,15,18] The addition of RBV to peg-IFN significantly increases the rate of SVR; however, in patients with thalassemia, RBV-associated hemolysis leads to an increased requirement for blood transfusions, which in turn can lead to worsening of iron overload.[1,14–16] Therefore, European Association for the Study of the Liver (EASL) 2016 guidelines recommend interferon-free regimens for the treatment of HCV infection in patients with hemoglobinopathies.[13]

Direct-acting antiviral drugs (DAAs) have demonstrated excellent efficacy in patients with HCV infection, with SVRs of >90% reported, irrespective of HCV genotype or response to previous therapy.[3,19,20] However, DAAs have not been extensively used in patients with hemoglobinopathies, and patients with hemoglobinopathies were excluded from pivotal clinical trials of DAAs in chronic HCV infection.[21] Current clinical data regarding the safety and efficacy of DAAs in patients with hemoglobinopathies and HCV infection are limited.[21–24]

The aim of this study was to evaluate the safety and efficacy of DAA regimens in patients with hemoglobinopathies and chronic HCV liver disease treated in Italy.

2 | METHODS

2.1 | Study design

Patients with hemoglobinopathies and HCV chronic disease from 11 thalassemia centers and who were treated with DAA regimens according to the Italian Medicines Agency guidelines[25] were included in the "THAlassemia and hepatitis C Advance - Società Italiana Talassemie ed Emoglobinopatie" (ITHACA-SITE) dataset. The chart review was approved by the Independent Ethics Committee at each participating center, with the coordinating committee being located in Genoa, Italy. All patients signed an informed consent to record their clinical and virological data in the database.

In the database, data were collected at baseline, at 4 weeks of therapy, at the end of treatment and at 12 weeks of follow-up. Data collected included levels of aspartate transaminase (AST), alanine transaminase (ALT), serum creatinine, and quantitative serum HCV RNA. Serum ferritin levels were evaluated at baseline and at 12 weeks of follow-up after the end of therapy. Clinical data regarding diabetes, kidney disease, heart disease, hypogonadotropic hypogonadism, hypothyroidism, osteoporosis, presence of cryoglobulins, esophageal varices and previous hepatocellular carcinoma were also recorded for each patient, as well as data regarding current therapy, including iron chelation therapy and previous antiviral therapy. All patients' therapies were assessed for potential drug—drug interactions between hepatitis drugs and other medications.[26] The number of transfused units per month was recorded before, during and at the end of treatment. Cardiac and hepatic iron overload was assessed with T2* magnetic resonance imaging (MRI). Liver fibrosis was assessed before the start of DAA therapy by FibroScan®(Echosens, Paris, France). A liver stiffness measurement (LSM) ≥12 kPa was used as the cut-off for the diagnosis of cirrhosis.

2.2 | Patients

Patients included in the study had hemoglobinopathies with chronic hepatitis due to HCV and the presence of fibrosis (defined as Fibroscan® stiffness ≥10 kPa) or cirrhosis (defined as Fibroscan® stiffness ≥12 kPa or through liver biopsy) determined within 6 months previously. Patients with extrahepatic manifestations of chronic HCV infection (cryoglobulinemia with organ damage, B-lymphoproliferative disorders) were also included. Patients with active cancer, including hepatocellular carcinoma, and pregnant or lactating females were not treated. A control group of patients with thalassemia major were also included in the study. These patients were HCV-RNA negative, without iron overload (according to MRI evaluation), and with compliance to iron chelation therapy of >80%. Liver iron overload was defined as MRI-T2* values less than 6.3ms and was categorized as mild (2.7-6.3 ms), moderate (1.4-1.6 ms), or severe (<1.4 ms).[27]

2.3 | Endpoints and outcomes measured

The primary endpoints of the study were to evaluate the efficacy and safety of DAAs in patients with hemoglobinopathies and chronic hepatitis or cirrhosis due to HCV.

Outcomes measured included the SVR rate (i.e., the proportion of patients with negative HCV RNA at week 12 of post-treatment follow up), and the effect of treatment on liver enzymes (changes from baseline in ALT, AST, and serum ferritin levels at the end of treatment and at week 12 of follow up). Baseline was defined as within the 30 days prior to receiving DAAs, and end of treatment was defined as 12 weeks after initiation of treatment. Follow up was conducted 12 weeks after the end of treatment (12-week follow up). Liver MRI-T2* evaluations were performed within 6 months of commencement of therapy.

2.4 | Statistical analysis

Descriptive statistics were summarized as means ± standard deviation (SD), medians, and percentages. To show the distribution of levels of ALT, AST, and ferritin at baseline, at the end of the treatment, and at 12 weeks of follow up, boxplot graphs were used. The Shapiro–Wilk test was used to test the normality of distributions. Changes in baseline levels of ALT, AST, and ferritin were compared at the end of treatment and/or after 12 weeks of follow up using the paired Wilcoxon test. The Wilcoxon test (unpaired) was also used to compare ferritin measurements between treated patients and the control group. Data were manipulated using Excel (Microsoft, Seattle, WA, USA), and statistical computing and graphics analyses were conducted using R software.[28]

TABLE 1 Patient demographics and clinical characteristics

	Patients ($n = 139$)
Age, years	
Mean (±SD)	42 (±7)
Range	30 − 68
Gender, n (%)	
Male	87 (63%)
Female	52 (37%)
Hemoglobinopathy, n (%)	
Thalassemia major	114 (82%)
Thalassemia intermedia	13 (9%)
Sickle cell disease	12 (9%)
HCV genotype, n (%)	
G1a	8 (5.8%)
G1b	91 (65.5%)
G2	25 (18.0%)
G3	7 (5.0%)
G4	7 (5.0%)
G5	1 (0.7%)
Liver−METAVIR Classification, n (%)	
F2	48 (34.5%)
F3	44 (31.7%)
F4	46 (33.1%)
Comorbidities, n (%)	
Heart disease	33 (24%)
Cryoglobulins	23 (17%)
Diabetes	20 (14%)
Kidney disease	5 (4%)
Previous antiviral treatment, n (%)	
Peg-INF + ribavirin	55 (40%)
Peg-INF	23 (17%)
None	61 (44%)
Liver iron overload, n (%)	
Mild (MRI-T2* values 2.7-6.3 ms)	12 (24%)
Moderate (MRI-T2* values 1.4-1.6 ms)	4 (8%)
Severe (MRI-T2* values <1.4 ms)	2 (4%)
None	33 (65%)

HCV, hepatitis C virus; MRI, magnetic resonance imaging; peg-IFN, pegylated interferon; SD, standard deviation.

3 | RESULTS

3.1 | Patients

Between March 2015 and December 2016, 157 patients were included in the ITHACA-SITE dataset. Of these, 139 (89%) met the study inclusion criteria and completed therapy and 12 weeks of follow up. Patient characteristics are summarized in Table 1. Mean (±SD) age was similar in males (41 ± 6 years) and females (44 ± 8 years). The majority of patients had thalassemia major (114 patients, 82%), 7 patients (5%) were affected by sickle-cell thalassemia, 3 patients (2%) by thalassemia intermedia and 1 patient (0.7%) by sickle-cell anemia. The most common HCV genotype was 1b (91, 65.5%). Almost all of the patients (138/139) had a LSM >10 kPa (34.5% F2, 31.7% F3, 33.1% F4) and in one patient cirrhosis was diagnosed histologically. More than half of the patients (56.1%) failed a previous antiviral treatment course with peg-IFN with or without RBV. By February 2017, all 139 patients (100%) had completed treatment and their post-treatment follow-up.

The mean level of serum ferritin was 1,450 ng/mL (range: 103-11,190 ng/mL) and liver iron overload was observed in 51 (37%) patients. Of these, 33 (65%) patients had moderate iron overload, 12 (24%) had mild iron overload and 6 patients (12%) had MRI-T2* measurements corresponding to moderate or severe liver iron overload.

The control group comprised 39 patients with thalassemia major. The mean age (±SD) of the control group was 35 (±9) years and the majority was female ($n = 25$). All controls were HCV-RNA negative and without iron overload (MRI-T2* >6.3 ms), with a mean ferritin level of 676 (±554) ng/mL (range 125–2537 ng/mL). The follow-up of the control group is greater than 24 months.

3.2 | Treatments

DAA therapy included sofosbuvir (SOF)-based regimens: SOF in combination with RBV (9%), SOF plus daclatasvir (DCV) (20%), SOF plus ledipasvir (LDV) with (9%) or without (38%) RBV, or SOF plus simeprevir (SMV) with (2%) or without (10%) RBV; or ombitasvir (OBV)/paritaprevir (PTV)-ritonavir plus dasabuvr (DBV) with (1%) or without (12%) RBV. Table 2 presents the DAA regimens according to HCV genotype.

The distribution of iron chelation regimens received by HCV patients before and during antiviral therapy, as well as the median doses administered, are reported in Supporting Information Table S1. Chelation therapy was changed to deferoxamine in 41 (29%) patients based on the previous studies of peg-IFN,[1] which reported that oral chelation therapy with deferoxamine was recommended for patients at risk of leucopenia and some physicians preferred treatment with deferoxamine as a precaution due to the lack of drug interaction data available. Iron chelation therapy was not prescribed in one patient with thalassemia major who had undergone allogeneic bone marrow transplantation and in patients affected by other hemoglobinopathies.

Patients received a wide range of concurrent therapies during the study. A description of concurrent therapies received by patients during anti-HCV treatment (other than chelation therapy) can be found in the Supporting Information Figure S1 and Table S2.

3.3 | Efficacy and safety

By intention-to-treat analysis, 136 patients (97.8%) achieved a response at end of treatment, and 130 (93.5%) achieved a SVR. In addition to the three patients who died during therapy or follow-up, six patients did not achieve HCV clearance. Five patients (one treated with SOF plus SMV, one treated with SOF plus DCV and three treated with SOF plus LDV) achieved virological response at the end of therapy and experienced relapses during the 12-week follow-up, one of these six patients did not achieve virological response on treatment with OBV/PTV plus DBV and at the end of the therapy had an HCV-RNA serum level of 20 IU/mL. These patients had increased levels of HCV-RNA during the follow up. All of these patients were treated for 12 weeks without RBV. SVR rates were high regardless of iron chelation therapy.

TABLE 2 Direct-acting antiviral regimens according to HCV genotype (total number of patients 139)

		Regimen (*n*)						
HCV genotype	Patients(*n*)[a]	SOF + SMV	SOF + DCV	SOF + LDV	OBV/PTV + DBV	SOF + RBV	RBV	24 weeks[b]
1a	8		1	6	1		3	3
1b	91	13	6	56	16		11	32
2	25		14			11	11	4
3	7		7				0	4
4	7	3		4			2	3
5	1	1					0	0

DBV, dasabuvir; DCV, daclatasvir; HCV, hepatitis C virus; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.
[a]*n*: number of patients.
[b]Duration of the treatment.

At 4 weeks 123/139 patients (88%) were HCV-RNA negative, 10/139 patients (7%) remained HCV-RNA positive, while data for six patients were missing. Figure 1 presents end of treatment virological response rate and SVR rate in the treated patients by HCV genotype.

There were no significant alterations in renal function laboratory measures. The blood transfusion requirement in the 3 months before therapy, during the therapy and 3 months after DAA therapy did not increase in patients who received DAA regimes without RBV (mean blood units transfused 3.8 vs. 3.7 vs. 3.8, respectively); however, as expected, the blood units requirement increased in patients treated with RBV (mean blood units transfused 3.6 vs. 5.5 vs. 4.0, respectively, $P < .001$).

Three patients died during treatment of causes unrelated to therapy. A 59-year-old woman with sickle-cell anemia and a history of anemia due to hematological disease died after 5 days of therapy with SOF plus SMV due to a hemolytic crisis followed by heart failure and cardiac shock. This death was unlikely to be related to treatment, as hemolytic anemia has not been reported in the literature with either of these antiviral drugs. A 36-year-old man with major thalassemia, diabetes, hypothyroidism, hypogonadism and severe heart disease died from secondary heart failure following bacterial sepsis. Finally, a 40-year-old man with Child-Pugh C cirrhosis died 4 weeks after the end of antiviral therapy died from liver failure after the appearance of a hepato-renal syndrome. Also, no interference with chelation therapy was observed, and no patients discontinued chelation therapy.

At the start of DAA treatment, only 29.2% of patients had normal serum ALT, while 86.7% and 92% had normal ALT at the end of treatment and 12 weeks thereafter, respectively. Reductions in serum ALT levels from baseline were statistically significant both at the end of treatment ($P < .001$) and at week 12 of follow up ($P < .001$; Figure 2).

At baseline the mean (±SD) value of serum ferritin was 1450 (±1660) ng/mL (range: 103 − 11,190 ng/mL). The mean (±SD) value of serum ferritin at the 12-week follow up after the end of treatment was 1080 (±1144) ng/mL (range: 88 − 5696 ng/mL) among patients who were HCV-RNA negative at Week 12 of treatment and the mean reduction from baseline to Week 12 was statistically significant (433 ng/mL, $P < .001$; Supporting Information Figure S2).

In the comparison of treated patients and the control group of patients without HCV infection and iron overload, mean baseline ferritin levels were significantly higher in the treated versus control group (mean difference: 773 ng/mL; $P = .002$), whereas at the 12-week follow

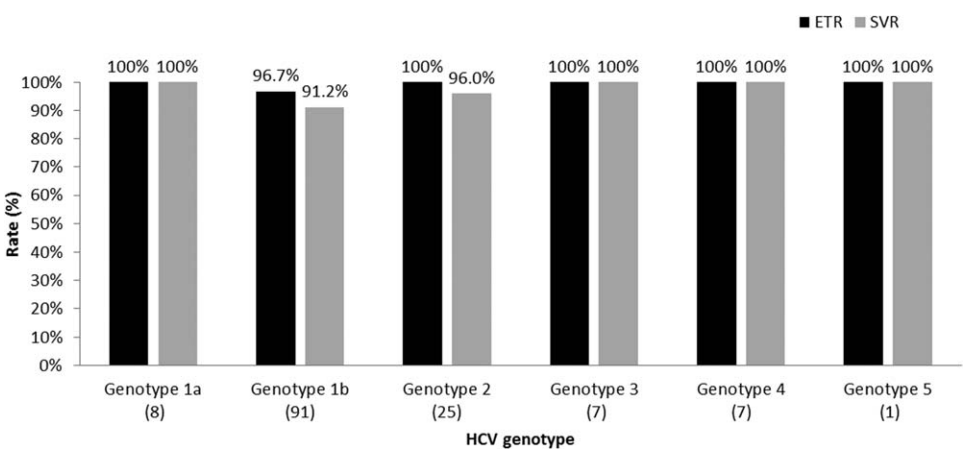

FIGURE 1 End of Treatment Response (ETR) and Sustained Virological Response (SVR) in patients with hemoglobinopathies and chronic HCV infection treated with DAAs

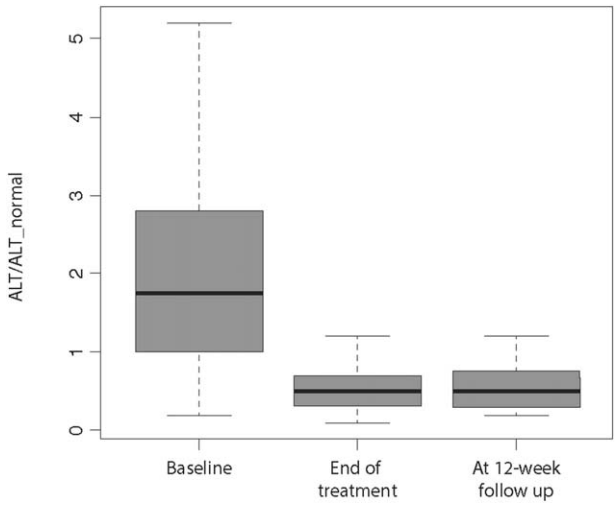

FIGURE 2 Median values and interquartile range ($25^{th}-75^{th}$ percentile) of the ratio of the serum levels of alanine transaminase (ALT) in respect to ALT normal levels at baseline, the end of treatment, and week 12 of post-treatment follow up

up, no statistically significant between-group differences were observed (mean difference: 385 ng/mL; $P=.21$).

4 | DISCUSSION

This is the largest observational study of DAAs in patients with hemoglobinopathies and HCV infection published to date. Until April 2017 in Italy, the use of DAA-based regimens was restricted to patients with advanced liver fibrosis or HCV-related severe extra-hepatic manifestations. Nevertheless, DAAs appeared to be safe and effective in this patient population in the current study. Patients showed high treatment response rates (SVR 93.5%), which were similar to those reported in patients without hemoglobinopathies.[3,19,20] Moreover, in our patient cohort, no treatment-related adverse events responsible for premature discontinuations were observed, and no overt drug-drug interactions between iron chelators and antivirals were reported. The three deaths that occurred during the observational period were due to complications of hematological or liver disease and not related to DAA therapy. As expected, patients showed a significant reduction in serum liver enzymes and ferritin. Moreover, ferritin levels in the treated patients at the follow up 12 weeks after the end of DAA therapy were not significantly different from those in the control group of patients with thalassemia without HCV infection or iron overload.

Our data confirm the finding of the multicenter phase III randomized trial of immediate or deferred treatment with elbasvir (EBR) plus grazoprevir (GRZ) in 159 patients with HCV infection and inherited blood disorders.[22] In that study, patients with thalassemia, sickle cell anemia, hemophilia A/B or von Willebrand disease were enrolled in 31 centers worldwide (US, Europe, Australia, Canada, Israel, and Thailand) and treated with a 12-week course of EBR plus GRZ. Among 107 patients who received immediate treatment, an SVR was achieved by 93.5% of the patients. The rate of serious adverse events unrelated to anti-HCV therapy was higher in patients who deferred treatment than in those who received immediate treatment (11.5% vs. 2.8%), suggesting an advantage of earlier treatment in these subjects.[22]

Higher SVR rates were reported in a smaller retrospective study of 81 patients with hemoglobinopathies (β-thalassemia major 86%, sickle cell anemia/β-thalassemia 14%) and HCV infection (38%) treated at a single institution in Greece between 2000 and 2015.[21] In that study, 11 patients received treatment with DAAs. Nine of them had failed a previous IFN-based course, and seven had severe fibrosis. All patients achieved SVR, and ferritin levels appeared to be reduced in most patients after treatment versus baseline.

Finally, in two case studies[23,24] two patients with hemoglobinopathies were successfully cured with SOF-based regimens. In the first case study, a 51-year-old female patient with HbS β 0-thalassemia was treated with SOF plus SMV, and achieved liver enzyme normalization, without any signs of hemolysis or need for blood transfusion.[24] In the second case study, a 16-year-old male affected by sickle thalassemia received 12 weeks' of SOF plus PegIFN.[23]

During the IFN-era, patients with hemoglobinopathies and HCV infection have largely been considered a "difficult-to-treat" population, due to the coexistence of liver iron overload, often associated with more advanced liver disease. The low response rates to IFN-based regimens have also led to patients with thalassemia being perceived as "difficult to cure," even with the newest DAA-based anti-HCV regimens.[21] In our study, the significant reduction of liver enzymes and ferritin associated with HCV elimination is clinically relevant, because they are two confounding factors in the management of patients with hematological disease. The levels of ferritin were reduced to those observed in a control group after HCV clearance. This may be due to the higher chelating efficacy of drugs in the liver that is not affected by inflammation. This finding confirms that ferritin is a more reliable marker in the monitoring of liver iron overload in patients without HCV infection. Long-term measurements of serum ferritin and of the liver and heart iron overload by MRI is needed to confirm this hypothesis. The continuation of iron chelation therapy during treatment with DAAs contributed to the reduction of ferritin. Most of our cohort of patients was infected with HCV before the 1990s, hence the higher mean age in the treated group of patients than in the control group. However, mean serum ferritin levels after treatment with DAAs were similar to the younger control group. These results add further support to EASL guidelines recommending the use of DAAs in selected patients with comorbidities, with careful monitoring for drug–drug interactions.[13]

The high number of enrolled patients, all followed for at least 3 months, is a particular strength of the study; it represents the largest observational population studied to date in this setting. However, the observational design is an obvious limitation of the current study.

Still, the use of RBV in patients with hemoglobinopathies infected with HCV requiring complex oral combination therapy continues to represent a treatment challenge since it is associated with a non-negligible risk of hemolityc anemia, with increases in both ferritin values and the need for blood transfusions. However, the availability of RBV-free regimens will further simplify the clinical management of this subgroup of patients.

In conclusion, the use of DAAs appears to be safe and effective in patients with hemoglobinopathies and cirrhosis or chronic hepatitis due to HCV. Treatment with DAAs was associated with a significant reduction of liver enzymes and serum ferritin, two confounding factors in the management of hemoglobinopathies. The lifetime utility of HCV eradication, in terms of reduction of liver complications and overall survival, requires evaluation in long-term observational cohorts.

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CONFLICT OF INTERESTS

Dr Origa has received honoraria from Novartis and Apopharma. Dr Filosa has received research funding from Novartis. Dr Piga has received research funding from Novartis and honoraria from Apopharma. Dr Saracco has participated in advisory boards under the sponsorship of Gilead, AbbVie, Bristol Myers Squibb, and Merck Sharp & Dohme. Dr Picciotto has participated in advisory boards under the sponsorship of AbbVie. Dr Cappellini has membership of the Board of Directors or advisory committees for Celgene, Genzyme-Sanofi, and Novartis. Dr D'Ambrosio has received honoraria for teaching and lecturing from Gilead, AbbVie, Bristol Myers Squibb, and Merck Sharp & Dohme, and has participated in advisory boards under the sponsorship of AbbVie and Gilead. Dr Di Marco has received research funding from Gilead. Dr Forni has received research funding from Novartis, Shire, and Celgene. Drs Ponti, Galeota Lanza, Pinto, Rigano, Madonia, Rosso, D'Ascola, Tartaglione, De Franceschi, and Gianesin have no relationships to disclose.

AUTHOR CONTRIBUTIONS

Study conception and design: G.L.F and V.D.M. Data Collection: R. O, M.L.P, A.F, A.G.L, A.P, G.M.S, V.P, A.P, P.R, S.M, R.M.R, D.D.A, M. D.C, R.D.A, I.T. Statistical analysis: B.G. Review and interpretation of results: G.L.F, V.D.M, R.O, M.L.P, A.F, A.G.L, A.P, G.M.S, V.P, A.P, P. R, S.M, R.M.R, D.D.A, M.D.C, R.D.A, I.T. Review for important intellectual content: G.L.F, V.D.M, R.O, M.L.P, A.F, A.G.L, A.P, G.M.S, V.P, A.P, P.R, S.M, R.M.R, D.D.A, M.D.C, R.D.A, I.T. All authors approved the manuscript before submission. G.L.F. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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