Anaemia predictors in patients with chronic hepatitis C treated with ribavirin and direct-acting antiviral agents

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ABSTRACT

Objectives Anaemia is the most common side effect associated with ribavirin (RBV). This study intended to assess its incidence and determine its predictive factors in patients with hepatitis C virus on RBV plus direct-acting antiviral agents (DAAs).

Methods A retrospective study of patients receiving RBV+DAA was conducted. Serum haemoglobin (Hb) was determined at baseline and monitored 4 weekly. Anaemia was defined as a single occurrence of Hb <10 g/dL. Bivariate and multivariate logistic regression analyses were conducted to assess the relationship between the occurrence of anaemia and the following factors: age, gender, FibroScan score, viral load, cirrhotic status (yes/no), RBV dose, glomerular filtration rate (GFR), alanine amino transferase, albumin, treatment duration (12 vs ≥12 weeks), baseline Hb, and Hb% drop (weeks 0–2).

Results 152 patients were included, of which 15.1% experienced anaemia. The analysis revealed that estimated GFR (eGFR), baseline Hb, 12-week treatment duration and Hb% drop (weeks 0–2) were significantly associated with the likelihood of developing anaemia ($p < 0.05$). Two mathematical models were subsequently developed to predict patients at risk of anaemia: a pretreatment model (positive predictive value 86.6%) which included eGFR, baseline Hb and 12-week treatment duration and an intratreatment model (positive predictive value of 90.48%) which in addition included the Hb% drop (weeks 0–2).

Conclusion Anaemia was found to be less significant in this cohort compared with studies on RBV plus pegylated interferon, telaprevir or boceprevir combinations, but higher than those on newer DAAs. Baseline Hb, eGFR, 12-week treatment duration and Hb% drop (weeks 0–2) significantly predicted the risk of anaemia and were used to construct two predictive models.

INTRODUCTION

Hepatitis C virus (HCV) is one of the main aetiological agents of chronic hepatitis, a condition that affects 160 million people worldwide.^{1,2} Long-term impact of HCV infection can vary markedly, ranging from minimal histological changes to cirrhosis with or without hepatocellular carcinoma.³

Until 2011, 24 or 48 week combination therapy with pegylated interferon (peg-IFN) plus ribavirin (RBV) was considered the gold standard in the treatment of chronically infected patients, obtaining sustained virological response (SVR) rates of 40%–50% in HCV genotype 1 (HCV-1) naive patients and around 80% in genotype 2 patients

(HCV-2), whereas genotypes 3 to 6 had intermediate SVRs.^{3,4}

In 2011, the protease inhibitors boceprevir and telaprevir were the first direct-acting antiviral agents (DAAs) to obtain marketing authorisation by the European Medicines Agency, in combination with peg-IFN+RBV.^{5–7} However, from 2014, they have been steadily superseded by more cost-effective and better tolerated drugs. Thus, new DAAs such as sofosbuvir (a pangenotypic RNA polymerase inhibitor), dasabuvir (a HCV-1-targeted RNA polymerase inhibitor), simeprevir and paritaprevir (HCV-1 and HCV-4 second-generation protease inhibitors), daclatasvir and ledipasvir (pangenotypic non-structural protein (non-structural protein 5A (NS5A)) inhibitors) and ombitasvir (HCV-1 and HCV-4 NS5A inhibitor) were approved for the treatment of HCV chronic infection, in many cases in combination with RBV. Current guidelines recommend RBV in combination with ombitasvir/paritaprevir/ritonavir plus dasabuvir for genotype 1a patients, in combination with ombitasvir/paritaprevir/ritonavir for patients with genotype 4 and in other combinations for patients with cirrhosis.⁸

Anaemia (defined as a haemoglobin (Hb) value <10 g/dL) is the most important side effect associated to RBV, though its incidence varies markedly: 20%–30% in patients treated with peg-IFN+RBV, 38% for telaprevir plus peg-IFN+RBV, and 50% for boceprevir plus peg-IFN+RBV.^{9–11} Furthermore, the relative incidences of anaemia for the newer DAAs were 10% for sofosbuvir/ledipasvir and between 7.5% and 10.5% for ombitasvir/paritaprevir/ritonavir plus dasabuvir, depending on treatment duration (12 or 24 weeks), respectively.^{12,13}

Prognostic factors for anaemia for patients receiving peg-IFN+RBV included renal function impairment and Hb drop below 1.5 g/dL on week 2.¹⁴ Another study revealed that factors such as female gender, age >50 years, body mass index <23 kg/m² and 28B CC interleukin genotype increased the risk in patients treated with telaprevir plus peg-IFN+RBV.¹⁵ These studies were conducted in patients treated with peg-IFN-based combinations over periods of 48 weeks or using stricter inclusion criteria in the case of newer DAAs.^{9–13} No study to date has evaluated the influence of these prognostic factors in real-world patients being treated with the newer DAAs. Thus, the objective of this study was to assess the incidence of anaemia as well as determining its predictive factors in a cohort of patients being treated with newer DAAs+RBV.

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METHODS

Study design

A retrospective study of patients who were treated with different combinations of RBV plus DAAs in a third-level teaching institution was conducted. The study was carried out from June 2015 to June 2016. Ethical approval was granted by the institutional ethics committee, in accordance with the Declaration of Helsinki (approval reference EMC-RIB-2016-01). Data were collected anonymously, and confidentiality was maintained through the use of numerical identifiers kept in an encrypted file.

Patients

Inclusion criteria: all adult patients with HCV genotypes 1–4, baseline weight between 40 and 125 kg and baseline viral load $>10\,000$ IU/mL,¹⁶ were included. None of the following constituted exclusion criteria: renal failure, decompensated cirrhosis and/or hepatitis B or human immunodeficiency viruses coinfection.

Study treatments

As per current guidelines, RBV doses were adjusted according to weight (1000 or 1200 mg/day for <75 or ≥ 75 kg, respectively). RBV dose was reduced to 800 mg/day in case Hb drops below 10 g/dL, and treatment was discontinued if Hb dropped below 8.5 g/dL.¹⁷

Study variables

Serum Hb was determined at baseline and monitored 4 weekly. Patients who experienced an Hb drop below 10 g/dL (and the week in which this occurred) were recorded. The maximum intratreatment Hb drop (defined as the difference between baseline and the lowest Hb level at any point during treatment) was also recorded. Hb levels at week 4 were used to estimate serum Hb levels at week 2 (by halving the difference between baseline and week 4). They were also used to calculate the percentage of Hb reduction between baseline and week 4. The resulting Hb% drop was included as a factor in the analysis. Other patient characteristics included age, gender, treatment combination received, RBV dose (1000 or 1200 mg/day), FibroScan score (transient elastography is a non-invasive, rapid and reproducible method allowing the evaluation of liver fibrosis with a value ≥ 14 kPa indicating presence of cirrhosis), viral load, grade of cirrhosis, estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, alanine aminotransferase (ALT), albumin, platelet count, treatment duration (12 and ≥ 12 weeks), naive/not naive status and baseline Hb. Finally, as an effectiveness variable, we used the number and percentage of patients with sustained virological response at 12 weeks (SVR12W).

Statistical analysis

In order to obtain a 5% accuracy, and assuming a rate of anaemia of 10% with a normal bilateral CI of 95%, it was determined that a total of 139 patients would be necessary. This figure was increased by 10% to overcome potential information loss during the study. Baseline characteristics of patients with and without anaemia were compared using Student's t-test or Mann-Whitney for continuous variables and χ^2 for categorical variables. Comparisons were deemed statistically significant if $p \leq 0.05$. A one-way analysis of variance test was conducted to verify the differences in Hb values at weeks 0, 4, 8 and 12. Bivariate and multivariate logistic regression analyses were conducted to assess the relationship between the potential predictive factors and the

occurrence of anaemia. Factors initially included in the bivariate analysis were age, gender, FibroScan score, cirrhotic status (yes/no), viral load, RBV dose, eGFR, ALT, albumin, treatment duration 12 versus >12 weeks, baseline Hb and Hb% drop (weeks 0–2).

For the forced-entry multiple regression model, factors were included whenever the previous bivariate χ^2 test result was significant (assuming level of significance ≤ 0.1). Additionally, factors were excluded from the analysis when Wald's χ^2 test results were not significant (assuming level of significance ≤ 0.05). ORs and 95% CI were calculated for anaemia predictive factors.

Two mathematical models were built using the factors that significantly predicted the risk of developing anaemia: the first model aimed at estimating the early risk of developing anaemia (prior to any treatment), whereas the second aimed at predicting the risk of developing anaemia after initiation of treatment (but before it occurred). The results obtained were compared with real patient data to calculate the positive and negative predictive values. Finally, the area under the receiver operating characteristic (ROC) curve was performed to determine the discrimination ability of such predictive models. All calculations were performed using the SPSS V.20.

RESULTS

One hundred and fifty-two patients who met the inclusion criteria were recruited over a year (baseline characteristics were summarised in [table 1](#)). Twenty-three patients (15.1%) experienced anaemia at some point throughout their treatment; four of them (2.63%) had serum Hb <8.5 g/dL, requiring treatment discontinuation. [Table 2](#) shows the compared baseline characteristics between patients who did and those who did not experience anaemia. Statistically significant differences between both groups were found in relation with the following characteristics: age ($p \leq 0.001$), gender ($p \leq 0.01$), eGFR ($p \leq 0.001$), platelet count ($p \leq 0.01$), albumin ($p \leq 0.01$), treatment duration >12 weeks ($p \leq 0.05$) and baseline Hb ($p \leq 0.001$).

Even though no significant differences were observed in the incidence of anaemia between patients with and without cirrhosis, none of the patients classed as F1 or F2 developed anaemia.

Anaemia occurred mostly during the first month of treatment (nine patients, see [figure 1](#)). Mean Hb drop during treatment was 2.67 g/dL (95% CI 2.45 to 2.9). Intratreatment mean Hb levels had shown statistically significant differences between weeks 0 and 12 ($p \leq 0.001$).

Such differences were more prominent between weeks 0 and 4, to stabilise progressively thereafter. Differences between patients with and without anaemia were statistically significant ($p \leq 0.001$), as depicted in [figure 2](#). The slope in the Hb drop between weeks 0 and 4 was more pronounced in patients with anaemia, whereas both curves behave similarly after week 4.

With regard to the effectiveness results, among our 152 patients treated with DAA and RBV 146 had SVR12W which resulted in 96.05% of effectiveness. It is noteworthy that none of the six patients with virological failure had anaemia during treatment.

Statistical analysis

As shown in [figure 3](#), the bivariate logistic regression analysis revealed that the following parameters were associated with the development of anaemia in patients treated with DAA+RBV: female gender, age, eGFR, albumin, treatment duration, baseline Hb and Hb% drop between weeks 0 and 2 ($p \leq 0.05$). Whereas there was no statistically significant relation between

Table 1 Baseline patient characteristics

Characteristics	152
Age, mean years (SD)	54.73 (8.60)
Sex, male, n (%)	119 (78.30)
FibroScan score, mean kPa (SD)	17.60 (9.99)
Fibrosis	
Non-cirrhotic, n (%)	57 (37.50)
F1	5 (3.30)
F2	17 (11.20)
F3	35 (23.00)
Cirrhotic, n (%)	
F4	95 (62.50)
GFR CKD-EPI, mean, mL/min (SD)	98 (16.81)
HCV RNA, $\times 10^6$ mean, copies/mL (SD)	2.79 (3.5)
Platelets, $\times 10^3$ mean, count/ μ L (SD)	157.99 (83.77)
Albumin, mean, g/dL (SD)	4.11 (0.50)
ALT, mean, U/L (SD)	83.11 (52.08)
Weight >75 kg, n (%)	73 (48.00)
Naive, n (%)	86 (56.60)
Treatment duration, 12 weeks/>12 weeks, n (%)	128/24 (84.20/15.80)
Baseline haemoglobin, mean g/dL (SD)	14.93 (1.62)
HCV genotype, n (%)	
1	102 (67.10)
2	5 (3.30)
3	24 (15.80)
4	21 (13.80)
Treatment associated to ribavirin, n (%)	
Sofosbuvir–ledipasvir	59 (38.80)
Ombitasvir–paritaprevir–ritonavir–dasabuvir	31 (20.40)
Sofosbuvir–simeprevir	17 (11.20)
Sofosbuvir–daclatasvir	18 (11.80)
Sofosbuvir	5 (3.30)
Sofosbuvir–pegylated interferon	10 (6.60)
Simeprevir–pegylated interferon	3 (2.00)
Ombitasvir–paritaprevir–ritonavir	9 (5.90)

ALT, alanine aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; HCV, hepatitis C virus.

the incidence of anaemia and the degree of cirrhosis, none F1 or F2 (n=22) patients experienced anaemia.

On the other side, only 4.3% of 115 patients with eGFR >90 mL/min experienced anaemia during their treatment (OR 0.05; 95% CI 0.02 to 0.14). Consequently, a baseline eGFR >90 mL/min determined a protective effect against anaemia.

Three pretreatment predictive factors for anaemia in patients receiving DAA+RBV were identified by the multiple logistic regression analysis (see table 3): eGFR, baseline Hb and treatment duration of 12 weeks. The previously obtained regression coefficients were used to build a pretreatment anaemia predictive model, which formula is:

$$P = 1/(1 + e^{-(21,583 - 0,098*(x) - 2,006*(y) - 0,915*(z))})$$

where p=probability of developing anaemia; x=eGFR (CKD-EPI); y (if 12-week treatment duration)=1; and z=baseline Hb. R^2 Nagelkerker=0.64. Positive and negative predictive values of 86.60% and 92.70%, respectively, were obtained. The discrimination capacity determined by the area under the ROC curve was 0.942 (95% CI (0.893 to 0.974)).

Table 2 Compared baseline patient characteristics

Parameter	Patient with Hb >10 g/dL (n=129)	Patient with Hb <10 g/dL (n=23)	p Value
Age, mean years (SD)	53.75 (7.64)	60.22 (11.44)	$p \leq 0.001^*$
Sex, male, n (%)	107 (82.90)	12 (52.20)	$p \leq 0.01^\dagger$
FibroScan, mean score (SD)	17.20 (17.20)	19.88 (19.89)	NS ‡
Cirrhosis, n (%)	78 (60.05)	17 (73.90)	NS ‡
GFR CKD-EPI, mean, mL/min (SD)	99.92 (11.03)	73.05 (24.33)	$p \leq 0.001^*$
HCV RNA, mean, $\times 10^6$ copies/mL (SD)	2.87 (3.70)	2.32 (2.46)	NS ‡
Platelets, mean, $\times 10^3$ count/ μ L (SD)	164.64 (86.10)	120.69 (57.57)	$p \leq 0.05^*$
Albumin, mean, g/dL (SD)	4.16 (0.47)	3.85 (0.59)	$p \leq 0.01^*$
ALT, mean, U/L (SD)	83.48 (52.70)	81.04 (49.52)	NS ‡
Weight >75 kg, n (%)	66 (51.20)	7 (30.40)	NS ‡
Naive, n (%)	73 (56.60)	13 (56.50)	NS ‡
Treatment duration >12 weeks, n (%)	16 (20.40)	8 (34.80)	$p \leq 0.05^\dagger$
Baseline haemoglobin, mean g/dL (SD)	15.29 (1.35)	12.88 (1.45)	$p \leq 0.001^*$

*Student's t-test.

$^\dagger \chi^2$ test.

‡ Mann-Whitney U test.

ALT, alanine aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; NS, non-significant.

Similarly (see table 3), an intratreatment mathematical model was constructed using data from table 3, the regression coefficients of baseline variables and the Hb% drop between weeks 0 and 2 (as an early indicator of anaemia), which formula is:

$$P = 1/(1 + e^{-(30,447 - 0,111*(a) - 2,924*(b) - 1,753*(c) + 0,28*(d))})$$

where p=probability of developing anaemia; a=eGFR (CKD-EPI); b (if 12-week treatment duration)=1; c=baseline Hb; and d=Hb% drop between weeks 0 and 2. R^2 Nagelkerker=0.8. Data from the resulting equation were compared with real data to obtain the positive and negative predictive values, which were 90.48% and 96.95%, respectively. The area under the ROC curve in this case was 0.978 (95% CI (0.940 to 0.995)).

Figure 1 Time to development of anaemia (haemoglobin <10 g/dL).

Figure 2 Comparable change in haemoglobin concentrations (g/dL) from start of treatment to week 12.

The comparison of the results predicted by this equations with real patient data concluded that the use of this pretreatment model would have prevented five out of nine anaemia episodes from occurring at week 4, and three-fourths of severe anaemia episodes (those with Hb < 8.5 g/dL). Likewise, the comparison of data from the second equation and real patient results showed that the use of this intratreatment model would have prevented all the episodes at an early stage (prior to week 4), as well as all cases of severe anaemia.

DISCUSSION

In recent years, the place of RBV in current therapeutics has changed from a central to a more complementary role. Thus, prior to commencement of treatment, clinicians involved in the management of chronically infected HCV patients can choose

from an array of non-RBV-containing regimens, or even the same alternative in extended duration modalities.⁸ Such strategies have allowed clinicians to anticipate and minimise the development of anaemia, resulting in no need for erythropoietin coadministration (which in turn carries an increased risk of neoplasias, thrombotic events or hypertension).^{18 19}

One of the key findings of this study was to determine the incidence and predictive factors of anaemia in a cohort of real-world patients (including human immunodeficiency virus coinfected and renally impaired patients) and compare them with previously reported studies. Despite more lenient inclusion criteria, this study found a lower incidence of anaemia (~15%) than studies on 48-week treatments with peg-IFN+RBV and significantly lower than studies in which telaprevir or boceprevir were added to the aforementioned combination (30%–50%).^{9–11} Arguably, shorter exposures to RBV and the fact that these drugs can increase per se the risk of anaemia might account for the lower anaemia rates observed in our study.

On the contrary, the incidence of anaemia was slightly higher than clinical trials with the newest DAAs (10% for sofosbuvir/ledipasvir and between 7.5% and 10.5% for ombitasvir/paritaprevir/ritonavir plus dasabuvir).^{12 13} On one side, the rationale for these higher rates could rely on the fact that peg-IFN was used in our cohort (in combination with the aforementioned DAAs) in 8.6% of cases (of which one patient developed anaemia). On the other side, although the renal function in the trials on sofosbuvir/ledipasvir and ombitasvir/paritaprevir/ritonavir plus dasabuvir was not disclosed, the fact that a fourth of the study population had mild or moderate renal failure could account for some of the differences.

The kinetics of the Hb decrease in this cohort was similar to those found with combinations of peg-IFN+RBV, in which the biggest drop occurred over the first 4 weeks, and achieved a plateau thereafter.^{9 14} Likewise, the same pattern was observed when the population of study was stratified into patients with and without anaemia, being the rate and speed of Hb drop more pronounced among the former.⁹

Figure 3 Outcome of the bivariate logistic regression analysis. ALT, alanine aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HCV, hepatitis C virus.

Table 3 Results of multiple logistic regression analysis (ribavirin-induced anaemia)

Parameter	Initial multivariate model			Final pretreatment multivariate model			Final on-treatment multivariate model		
	RC	p Value*	OR (95% CI)	RC	p Value*	OR (95% CI)	RC	p Value*	OR (95% CI)
Albumin (per g/dL)	−0.39	NS	0.68 (0.13 to 3.55)						
Dose (1000 mg/1200 mg)	0.14	NS	1.15 (0.13 to 10.19)						
CKD-EPI (per mL/min)	−0.11	≤0.01	0.90 (0.83 to 0.97)						
Treatment duration (12 weeks)	−2.94	≤0.05	0.05 (0.04 to 0.70)	−2.01	≤0.05	0.13 (0.02 to 0.76)	−2.94	≤0.05	0.05 (0.01 to 0.53)
Baseline Hb (per g/dL)	−1.71	≤0.01	0.18 (0.06 to 0.53)	−0.91	≤0.001	0.40 (0.24 to 0.65)	−1.75	≤0.01	0.17 (0.06 to 0.48)
Week 2 from baseline Hb change % (per g/dL)	0.64	≤0.01	1.89 (1.28 to 2.79)				0.63	≤0.01	1.87 (1.27 to 2.75)

*Wald's χ^2 test.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; NS, non-significant; RC, regression coefficient.

As reported by Zeuzem *et al*, the bivariate analysis showed that variables such as female gender, age and baseline Hb, were associated to the occurrence of anaemia.¹¹ The eGFR was also associated with a higher risk of anaemia, as what occurred in the study by Reau *et al*.¹⁴ Albumin, treatment duration and Hb% drop between weeks 0 and 2 were as well associated to the occurrence of anaemia, even though such variables were not included in the aforementioned studies. On the other hand, the cirrhotic status was not associated to the development of anaemia. This is also in line with the study by Zeuzem *et al*.¹¹ In spite of this, none of the patients classed as F1 or F2 developed anaemia. The FibroScan score, the baseline viral load and ALT were not associated to the development of anaemia either. In contraposition, an eGFR value >90 mL/min was associated to a lower risk of anaemia.

An association was also found between the risk of experiencing anaemia and factors such as baseline Hb, treatment duration of 12 weeks, Hb% drop between weeks 0 and 2 and eGFR, according to the multiple regression analysis. On the contrary, albumin and RBV dose did not show significant relations with regard to the appearance of anaemia. The relationship between the risk of anaemia and baseline Hb found in this study had been previously suggested by other authors, such as Reau *et al* and Zeuzem *et al*.^{11 14} The present study also revealed that

a treatment duration of 12 weeks (as opposed to >12 weeks) was also linked to a lower occurrence of anaemia. To date, no study has assessed the relationship between them, arguably due to the fact that studies evaluating anaemia in patients receiving peg-IFN+RBV with or without boceprevir or telaprevir had normally longer treatment durations. Age and gender (which showed a statistically significant association with anaemia in the bivariate analysis) were not included in the multivariate analysis. The rationale for this relied on the fact that their use in the eGFR calculation could lead to colinearity bias. This approach is similar to the study by Reau *et al*, who also included eGFR as a variable in the analysis, observing that the relation between the risk of anaemia and age and gender was not significant.¹⁴ This could explain why studies not including eGFR did find a positive association between age and gender and the risk of anaemia.^{11 20}

Regarding this association between chronic kidney disease, RBV and anaemia is widely assumed that RBV-induced anaemia primarily results from increased RBV concentrates in a red blood cell (RBC), which causes a relative ATP deficiency and increased susceptibility to oxidative damage, leading to accelerated RBC turnover and haemolytic anaemia.²¹

The second key finding of this study was the development of two predictive models using the positive and negative predictive factors previously mentioned. The applicability of these models relies on their use as pretreatment and early intratreatment tools to aid the selection of the appropriate therapy. In order to minimise the risk of anaemia, the following strategy is recommended: the pretreatment model is to be used prior to initiation of treatment so that if the model predicts a risk of anaemia (positive predictive value 86.60%), non-RBV alternative treatments should be recommended. This strategy would have prevented five out of nine anaemia episodes from occurring at week 4, and three-fourths of severe anaemia episodes (those with Hb <8.5 g/dL). The second predictive model is intended to be used in those patients in whom the pre-treatment model did not predict the development of anaemia. If the intratreatment model predicts a high risk of anaemia (positive predictive value 90.48%), a dose reduction or a treatment extension without RBV (from 12 to 24 weeks) should be recommended. The application of this strategy would have prevented all the anaemia episodes at an early stage (prior to week 4), as well as all cases of severe anaemia. The concomitant use of both predictive models would result in a marked reduction in the episodes of anaemia and therefore a safer RBV treatment (see online supplementary figure 1). This approach might also have little influence on the effectiveness of the treatment given the fact that all the patients with anaemia and whose RBV doses were reduced reached SVR12W.

What this paper adds

What is already known on this subject

- ▶ Anaemia is the most common side effect associated with ribavirin (RBV).
- ▶ Its incidence varies markedly: 20%–30% in patients treated with pegylated interferon (peg-IFN)+RBV, 38% for telaprevir plus peg-IFN+RBV and 50% for boceprevir plus peg-IFN+RBV.
- ▶ These studies were conducted in patients treated with peg-IFN-based combinations over periods of 48 weeks.

What this study adds

- ▶ This study has studied the incidence of anaemia in a cohort of real-world patients being treated with newer direct-acting antiviral agents in combination with RBV. This landscape is new with lower duration of treatments and peg-IFN-free combinations.
- ▶ Finally we have constructed two models (pretreatment and early on-treatment models) that predict those patients at risk of anaemia when RBV is going to be used in combination with newer direct-acting antiviral agents.

Caveats associated with this study rely on the fact that 8.6% of patients included in this cohort were also on peg-IFN (in combination with RBV plus either sofosbuvir or simeprevir for genotype 3 as per current guidelines, in 6.6% and 2% of cases, respectively). However, only one case of anaemia occurred among these patients, in a patient with eGFR <40 mL/min, whereas all other patients in peg-IFN-based combinations had eGFR >90 mL/min. Therefore, it is unlikely that the results of this study were affected by the coadministration of peg-IFN.

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Contributors EM-C had the first conception and was the coordinator of the study; he also has taken part in the design, acquisition of data, statistical analysis and interpretation of the data. On the other hand, he wrote the first draft of the article. HM-C collaborated in developing the design, analysis, interpretation of the results and made an important critical revision. AC and MCM have participated in the acquisition and interpretation of data. They also have contributed with their technical support in all aspects of the study related to their clinical specialties. All the authors have made a critical revision of the manuscript and have approved the final version; they also have agreed to account for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no unpublished data from the study.

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