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ORIGINAL ARTICLE

Ropeginterferon phase 2 randomized study in low-risk polycythemia vera: 5-year drug survival and efficacy outcomes

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Abstract

In patients with low-risk polycythemia vera, exposure to low-dose Ropeginterferon alfa-2b (Ropeg) 100 µg every 2 weeks for 2 years was more effective than the standard treatment of therapeutic phlebotomy in maintaining target hematocrit (HCT) (< 45%) with a reduction in the need for phlebotomy without disease progression. In the present paper, we analyzed drug survival, defined as a surrogate measure of the efficacy, safety, adherence, and tolerability of Ropeg in patients followed up to 5 years. During the first 2 years, Ropeg and phlebotomy-only (Phl-O) were discontinued in 33% and 70% of patients, respectively, for lack of response (12 in the Ropeg arm vs. 34 in the Phl-O arm) or adverse events (6 vs. 0) and withdrawal of consent in (3 vs. 10). Thirty-six Ropeg responders continued the drug for up to 3 years, and the probability of drug survival after a median of 3.15 years was 59%. Notably, the primary composite endpoint was maintained in 97%, 94%, and 94% of patients still on drug at 3, 4, and 5 years, respectively, and 60% of cases were phlebotomy-free. Twenty-three of 63 Phl-O patients (37%) failed the primary endpoint and were crossed over to Ropeg; among the risk factors for this failure, the need for more than three bloodletting procedures in the first 6 months emerged as the most important determinant. In conclusion, to improve the effectiveness of Ropeg, we suggest increasing the dose and using it earlier driven by high phlebotomy need in the first 6 months post-diagnosis.

Keywords Polycythemia vera · Low-risk · Ropeginterferon alfa-2b · Phlebotomy

Introduction

In recent years, there has been a renewed interest in interferons for the treatment of myeloproliferative neoplasms (MPNs), [1, 2] mainly due to the development of pegylated versions such as pegylated interferon alfa-2a (Pegasys), pegylated interferon alfa-2b (PegIntron), and Ropeginterferon alfa-2b (Besremi). In particular, the monopegylated form of Ropeginterferon alfa-2b allows for less frequent dosing and improved tolerability compared to interferon alfa-2a and pegylated interferon alfa-2b, both of which have multiple pegylation sites. [3] Recent data have also shown that interferons have preferential activity against the hematopoietic stem cell clone, [4, 5] leading to complete hematological and clinical responses and the induction of molecular responses in a sizeable proportion of patients. Based on evidence from randomized clinical trials [6] and supported by observational studies, [7–9] Ropeginterferon alfa-2b (Ropeg) is now approved for the treatment of adults with PV in the USA and in Europe in PV without splenomegaly.

In a phase 2 randomized trial (Low-PV), Ropeg at a fixed dose of 100 µg every 2 weeks demonstrated clear superiority over standard therapy in maintaining hematocrit (HCT) levels on target. [10, 11] In the core trial segment, the Ropeg group achieved the primary endpoint measured at 1 year as HCT < 45% without progression events in 81% of cases,

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compared to 51% in the phlebotomy-only (Phl-O) group. Disease progression, defined by the protocol as symptomatic microvascular complications, major thrombosis, progressive leukocytosis, and thrombocytosis, occurred only in the phlebotomy group in 13% of patients and led to the initiation of cytoreduction in all patients. Patients were categorized as responders (meeting the primary endpoint) or non-responders and entered the extension phase of the trial (2nd year), the former continuing the treatment assigned at randomization ($n=52$ Ropeg and $n=32$ phlebotomy-only) while the latter switched to the alternative group ($n=23$ from Phl-O to Ropeg and $n=9$ from Ropeg to Phl-O). The safety and efficacy profile of Ropeg, assessed for all patients treated for 24 months in both the core and extension phases, was favorable. These promising results by Ropeg were accompanied by a significant reduction in the need for phlebotomy procedures, decreased *JAK2*V617F allele burden, no thrombotic events, no progression of leukocytosis, and improved quality of life.

The Low-PV study started enrolling the first patients in 2017. As previously reported, [10, 11] enrollment was stopped by the data safety monitoring board after the second interim analysis due to overwhelming efficacy, resulting in 127 patients completing 2 years of follow-up as per protocol instead of the 150 calculated in the original protocol sample size. A further amendment to the protocol was approved by our IRB to extend the study only to patients still on Ropeg at the end of the 2-year period to March 31, 2023, the planned end of the study.

This report focuses on one of the most important aspects of interferon treatment, namely drug survival, defined as a proxy measure for the effectiveness, safety, adherence, and tolerability of a medicine. [12] To address this issue, we estimated the drug survival during the extended observation period of up to 5 years and efficacy outcomes in patients who continued to use the drug in the continuation phase lasting up to 5 years. In addition, we investigated the factors leading to the discontinuation of phlebotomy procedures in patients of the Phl-O group and crossing over to the Ropeg treatment.

Methods

The Low-PV protocol was approved by the institutional review board or central ethics committee of each participating center and all enrolled patients gave written informed consent.

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Drug survival was assessed using the Kaplan–Meier (KM) curve and defined as the time from drug initiation to discontinuation for any reason (whether due to safety concerns or ineffectiveness). The efficacy of Ropeg in maintaining HCT levels within the desired range (< 45%) and its impact on reducing the need for phlebotomy were assessed in patients who continued to receive the drug for 3, 4, and 5 years after randomization. The differences between responders and non-responders in the Phl-O arm were tested using chi-squared tests and Wilcoxon-Mann–Whitney tests for categorical and continuous variables, respectively.

Results

Ropeg survival

One hundred and forty-six patients with low PV were screened for eligibility and 19 were excluded from randomization for various reasons as previously reported. [10, 11] Sixty-three low-risk patients were randomized to the standard Phl-O arm and 64 to the Ropeg arm. During the first 2 years of the trial, patients on Ropeg discontinued the drug in 33% and this occurred with major frequency in the first than in the second year. Patients randomized to Phl-O withdrew the procedures in 49% in the first year after randomization, and at the end of the second year, 70% of Phl-O cases discontinued this treatment (Fig. 1A). Reasons for drug and phlebotomy discontinuation are detailed in Table 1 and were mainly due to lack of response and withdrawal of consent in patients randomized to Phl-O.

The Ropeg survival probability estimated by Kaplan–Meier analysis was 72% (95% confidence interval (CI) 59–81%) at 2 years and declined to 58% (95% CI 43–70%) at 5 years (Fig. 1B). The two main reasons for discontinuation were failure to control HCT on target in 12/64 cases (19%) and the occurrence of adverse events in 9/64 patients (14%); discontinuation was voluntary in three patients (5%) and due to progression of leukocytosis ($n=1$, 1.5%) and overt myelofibrosis ($n=1$, 1.5%).

Efficacy outcomes up to 5 years

Patients who completed the trial and who responded to Ropeg ($n=36$) continued to receive the drug until the end of the continuation phase (March 31, 2023). The dose of the drug remained unchanged (100 µg every 2 weeks) and, at follow-up, phlebotomies were performed if HCT exceeded 45%, just as in the first 2 years of the trial. All patients also continued to receive low-dose aspirin (100 mg/day). The median time on treatment was 3.15 years (range 0.04–5.77). In Fig. 1C, we report the percentage of patients who maintained the response in the third, fourth, and fifth years,

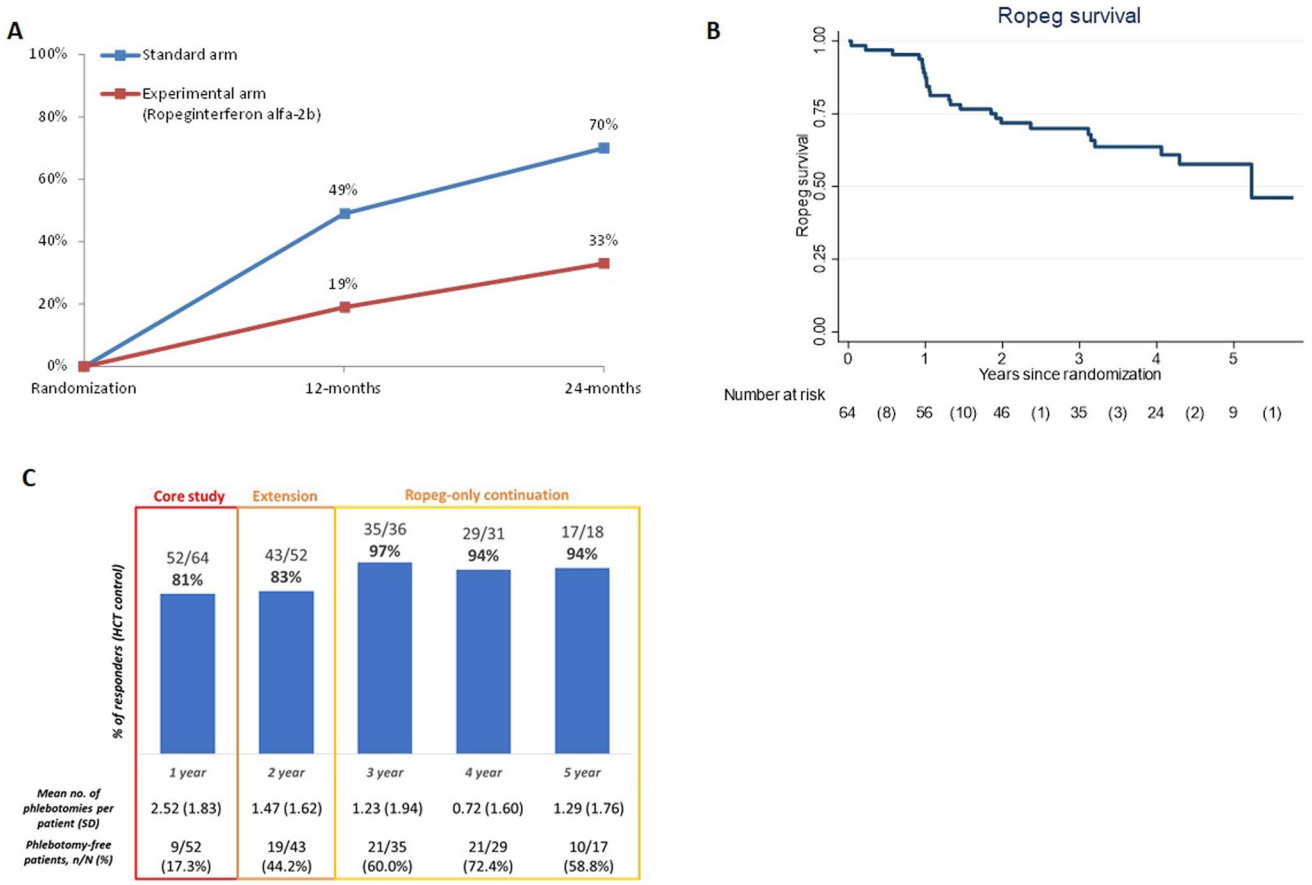

Fig. 1 Percentage of treatment discontinuation by randomized arms at 12 and 24 months (**A**); overall Ropeg treatment survival (**B**) and hematocrit control over 5 years (**C**)

Table 1 Reasons for treatment discontinuation at 1 and 2 years by treatment assigned at randomization

Discontinuations, *n* (%)	Ropeg arm (*N* = 64)	Phlebotomy-only arm (*N* = 63)
1 year	12 (19%)	31 (49%)
No response	9 (14%)	29 (46%)
*Adverse event**	3 (5%)	-
Withdrawal of consent	-	2 (3%)
2 year	9 (14%)	13 (21%)
No response	3 (5%)	5 (8%)
*Adverse event***	3 (5%)	-
Withdrawal of consent	3 (5%)	8 (13%)
Total	21 (33%)	44 (70%)

*Asthenia (*n* = 1), increased transaminases (*n* = 1), pruritus (*n* = 1)

**Thyroid disorder (*n* = 1), metrorrhagia (*n* = 1), neutropenia (*n* = 1)

respectively. The target HCT in the absence of progression of leukocytosis, thrombocytosis, and vascular complications was maintained in 97%, 94%, and 94% at 3, 4, and 5 years, respectively. This result was associated with freedom from phlebotomy in a percentage of patients equal to or greater than 60%.

Switch from phlebotomy to Ropeg

The switch from phlebotomy to Ropeg is a critical aspect of the present study as it allowed us to identify a group of patients who were resistant to a rigid phlebotomy program of monthly visits and blood draws of 300–400 mL when HCTs were > 45%. The reasons for cross-over involved 23/63 patients (37%) randomized to the Phl-O group, and were exclusively due to failure to achieve the primary combined endpoint which, as previously mentioned, included achieving the HCT target in the absence of vascular complications or progression of leukocytosis and thrombocytosis. In the group of non-responders, in addition to the 23 patients, we also included 8 patients who, in the first 12 months from randomization, left the study due to early disease progression (*n* = 6) or withdrawal of consent (*n* = 2). Thus, a total of 31 non-responders to phlebotomy were examined for clinical and laboratory characteristics. They were more likely to be male (74%) ($p = 0.048$), had

a higher prevalence of hypercholesterolemia (29% vs 1%, $p = 0.010$), tended to have a higher body mass index (25.5 vs. 23.0, $p = 0.091$), and required a median of three phlebotomies per patient in the first 6 months (interquartile range (IQR) 2–4), which increased to five phlebotomies (IQR 3–7) over the first 12 months. Interestingly, in non-responders crossing over to Ropeg (23/31), this drug was less efficacious (30%) in comparison with the results achieved when administered at randomization and phlebotomy requirement remained consistently high (median 5, IQR 2–7). In contrast, a median of one phlebotomy per patient (IQR 0–2) was required in responders in the first 6 months and the demand for bloodletting settled at two procedures thereafter (Fig. 2). Throughout the entire study, the number of phlebotomies in the two groups was 156 vs. 85 procedures, with a marked difference seen as early as 6 months. The two groups also showed different trends in white blood cell (WBC) counts: non-responders had significantly higher median values over time (approximately 13×10^9/L) compared to responders (10×10^9/L) ($p < 0.001$), while there were no significant differences in platelet counts and *JAK2*V617F allele burden between the groups.

The different need for phlebotomy in the first 6 months and thus the existence of two groups based on the number of phlebotomies to maintain HCT < 45% was confirmed in the Spanish PV registry including 100 low-risk patients. In comparison with those requiring three or more phlebotomies ($n = 79$), the group with no more than two phlebotomies within 6 months of diagnosis ($n = 21$) showed a lower JAK2 allele burden (VAF of 21% and 34% in responders and non-responders, respectively, $p = 0.06$) and lower need for starting cytoreduction due to inadequate HCT control or leukocytosis (0% and 13% in responders and non-responders, respectively, $p = 0.048$).

Discussion

In patients assigned to Ropeg, drug survival was primarily influenced by two key factors, lack of response ($n = 14$, 22%) and the occurrence of adverse events, which were observed in nine (14%) of patients followed up to 5 years. This valuable information provides important insights for making more informed decisions about treatment plans for patients with low-risk polycythemia vera (PV). It is highly likely that the fixed low dose of 100 µg administered every 2 weeks is not sufficient to improve treatment efficacy and that an escalated dose of Ropeg, as used in the Proud Continuation study (reference), may be a more favorable approach to increasing the proportion of patients achieving the composite outcome, including maintaining HCT within the target range without disease progression. However, it is important to acknowledge the possibility of an increase in adverse events, although this seems unlikely based on the results of the Proud Continuation study. In this study, the average dose of Ropeg was four to five times higher than in our study and yet the incidence of drug discontinuation due to adverse events was 13%, a figure similar to that observed in the Low-PV study (14%). Therefore, a study demonstrating the greater efficacy of Ropeg at escalated doses, while minimizing the causes of discontinuation, would lead to an improvement in drug survival and promising results, as we have shown after 5 years of observation, albeit in a limited number of cases.

In addition, the experience of patients randomized to Phl-O may suggest another way to improve response and drug survival. In our study, patients treated with Phl-O who failed after 1 year of therapy were switched to Ropeg. We have shown that risk factors for non-response include a high need for bloodletting in the first 6 months, and therefore, the proposal to treat these patients earlier with Ropeg at

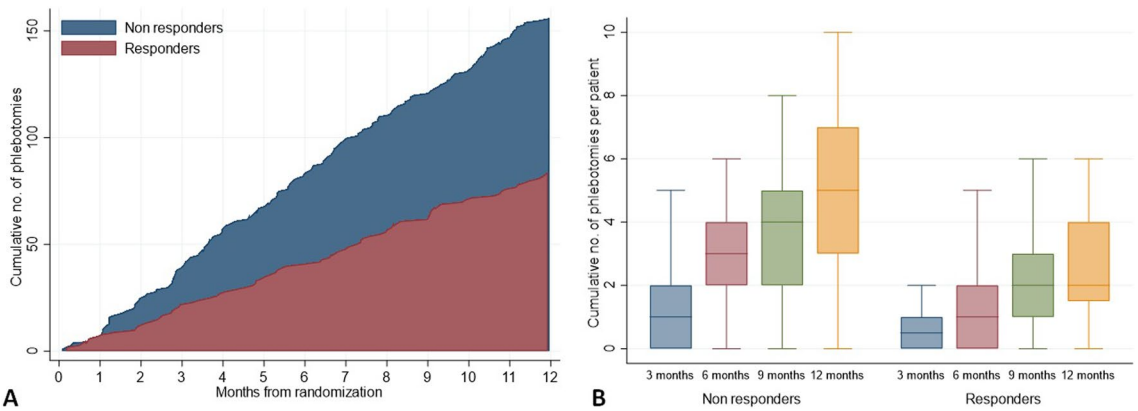

Fig. 2 Total (**A**) and per-patient (**B**) cumulative number of phlebotomies from randomization in phlebotomy-only arm, by responders and non-responders

escalated doses after observation for 6 months from diagnosis could increase response rates and greater long-term benefit.

Author contribution TB conceived and designed the study, supervised the analysis, and wrote the paper. AC performed statistical analysis and contributed to manuscript writing. FF was in charge of project and data management. AG and GC critically revised the data analysis. AMV revised the study and contributed to manuscript writing. LC and FG were in charge of the management of samples for the biological subproject. AAL collected and analyzed data for the validation set from the Spanish registry. VDS, ERo, FC, MBo, AI, FPal, GB, FPan, ARi, GC, MC, DR, CM, SS, ERu, AP, NC, BM, EC, GGL, PG, SB, FR, FL, LS, CB, DC, NV, MBe, MCF, GT, and ARa collected data. All authors revised and approved the final version of the manuscript.

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Data availability No shared data are available.

Declarations

Conflict of interest The authors declare no competing interests.

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