THE LANCET
Haematology

ARTICLES | VOLUME 7, ISSUE 3, E196-E208, MARCH 01, 2020

Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study

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Published: January 31, 2020 • DOI: https://doi.org/10.1016/S2352-3026(19)30236-4 •

Summary

Background

The PROUD-PV and CONTINUATION-PV trials aimed to compare the novel monopegylated interferon ropeginterferon alfa-2b with hydroxyurea, the standard therapy for patients with polycythaemia vera, over 3 years of treatment.

Methods

PROUD-PV and its extension study, CONTINUATION-PV, were phase 3, randomised, controlled, open-label, trials done in 48 clinics in Europe. Patients were eligible if 18 years or older with early stage polycythaemia vera (no history of cytoreductive treatment or less than 3 years of previous hydroxyurea treatment) diagnosed by WHO's 2008 criteria. Patients were randomly assigned 1:1 to ropeginterferon alfa-2b (subcutaneously every 2 weeks, starting at 100 µg) or hydroxyurea (orally starting at 500 mg/day). After 1 year, patients could opt to enter the extension part of the trial, CONTINUATION-PV. The primary endpoint in PROUD-PV was non-inferiority of ropeginterferon alfa-2b versus hydroxyurea regarding complete tological response with normal spleen size (longitudinal diameter of ≤12 cm for wom ı) at 12 months; in CONTINUATION-PV, the coprimary endpoints were complete haem

response with normalisation of spleen size and with improved disease burden (ie, splenomegaly, microvascular disturbances, pruritus, and headache). We present the final results of PROUD-PV and an interim analysis at 36 months of the CONTINUATION-PV study (per statistical analysis plan). Analyses for safety and efficacy were per-protocol. The trials were registered on EudraCT, 2012-005259-18 (PROUD-PV) and 2014-001357-17 (CONTINUATION-PV, which is ongoing).

Findings

Patients were recruited from Sept 17, 2013 to March 13, 2015 with 306 enrolled. 257 patients were randomly assigned, 127 were treated in each group (three patients withdrew consent in the hydroxyurea group), and 171 rolled over to the CONTINUATION-PV trial. Median follow-up was 182·1 weeks (IQR 166·3–201·7) in the ropeginterferon alfa-2b and 164·5 weeks (144·4–169·3) in the standard therapy group. In PROUD-PV, 26 (21%) of 122 patients in the ropeginterferon alfa-2b group and 34 (28%) of 123 patients in the standard therapy group met the composite primary endpoint of complete haematological response with normal spleen size. In CONTINUATION-PV, complete haematological response with improved disease burden was met in 50 (53%) of 95 patients in the ropeginterferon alfa-2b group versus 28 (38%) of 74 patients in the hydroxyurea group, p=0·044 at 36 months. Complete haematological response without the spleen criterion in the ropeginterferon alfa-2b group versus standard therapy group were: 53 (43%) of 123 patients versus 57 (46%) of 125 patients, p=0·63 at 12 months (PROUD-PV), and 67 (71%) of 95 patients versus 38 (51%) of 74 patients, p=0·012 at 36 months (CONTINUATION-PV). The most frequently reported grade 3 and grade 4 treatment-related adverse events were increased γ-glutamyltransferase (seven [6%] of 127 patients) and increased alanine aminotransferase (four [3%] of 127 patients) in the ropeginterferon alfa-2b group, and leucopenia (six [5%] of 127 patients) and thrombocytopenia (five [4%] of 127 patients) in the standard therapy group. Treatment-related serious adverse events occurred in three (2%) of 127 patients in the ropeginterferon alfa-2b group and five (4%) of 127 patients in the hydroxyurea group. One treatment-related death was reported in the standard therapy group (acute leukaemia).

Interpretation

In patients with early polycythaemia vera, who predominantly presented without splenomegaly, ropeginterferon alfa-2b was effective in inducing haematological responses; non-inferiority to hydroxyurea regarding haematological response and normal spleen size was not shown at 12 months. However, response to ropeginterferon alfa-2b continued to increase over time with improved responses compared with hydroxyurea at 36 months. Considering the high and durable haematological and molecular responses and its good tolerability, ropeginterferon alfa-2b offers a valuable and safe long-term treatment option with features distinct from hydroxyurea.

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Article Info

Publication History

Published: January 31, 2020

Identification

DOI: https://doi.org/10.1016/S2352-3026(19)30236-4

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