Evaluating the Feasibility of a Network Meta-Analysis Comparing Treatment Options in Polycythemia Vera

Andrew Howe, PharmD[1], Noemi Hummel, PhD[2], Claudia Castro, MS, PharmD[3], Agnieszka Kopiec, MSc[4], Hung Lun Chien, MPH[3]

[1]PharmaEssentia, Burlington, MA, USA, [2]Certara GmbH, Lörrach, Germany, [3]Former Employee PharmaEssentia, Burlington, MA USA, [4]Certara, Krakow, Poland

andrew_howe@pharmaessentia.com

KEY FINDINGS & CONCLUSIONS

- Network meta-analysis (NMA) for a rare disease like polycythemia vera (PV) was not feasible to conclude due to heterogeneity among studies including the population of interest, treatments, outcome definitions, length of follow-up and potential treatment effect modifiers.
- These published finding are valuable to share during rare disease formulary evaluations utilizing NMA to assess comparative clinical evidence when head-to-head clinical trial data is absent.

INTRODUCTION

- Polycythemia vera (PV) is a rare, chronic hematologic malignancy characterized by excessive red blood cell production mainly due to mutations in the JAK2 gene.
- This overproduction increases blood viscosity, elevating the risk of thromboembolic events, cardiovascular complications, and progression to myelofibrosis or acute myeloid leukemia.[1,2]
- PV significantly impacts patient outcomes, leading to a substantial disease burden and reducing overall quality of life.[3]
- While several treatment options exist to manage hematocrit levels and reduce thrombotic risks, the optimal treatment strategy remains uncertain.
- The current standard treatments for PV include phlebotomy alone (Phleb) or cytoreductive therapy, including hydroxyurea (HU), ruxolitinib (RUX), peginterferon-alfa-2a (PEG), and ropeginterferon-alfa-2b (ROPEG), with or without Phleb.
- Ropeginterferon-alfa-2b, a newly designed interferon, was approved to treat PV in the US in Oct 2021. The comparative effectiveness of existing interferons and JAK inhibitors remains unclear due to the absence of direct head-to-head clinical trials.

OBJECTIVE

- Perform a targeted literature review (TLR) to gather evidence from clinical trials and real-world studies on the efficacy and safety of PV treatments
- Assess feasibility of a network meta-analysis (NMA) indirectly comparing ropeginterferon alfa-2b to peginterferon alfa-2a or ruxolitinib, using standard of care as the common comparator

METHODS

- A TLR (date of search: May 9, 2024) screened clinical comparative evidence on PV treatments between May 2014 and May 2024 from PubMed and relevant conference abstracts, see **Table 1** for the PICOS scheme defining the inclusion criteria.
- Key clinical endpoints assessed in the TLR included complete hematologic response (CHR), molecular response, allele burden reduction, event-free survival, and safety outcomes such as adverse events and thromboembolic/thrombotic events.
- Feasibility of performing an NMA for these endpoints, ensuring NMA assumptions such as the homogeneity of trial populations and endpoint definitions are met, was assessed.
- Availability and comparability of outcomes across studies was assessed to enable the construction of treatment networks.

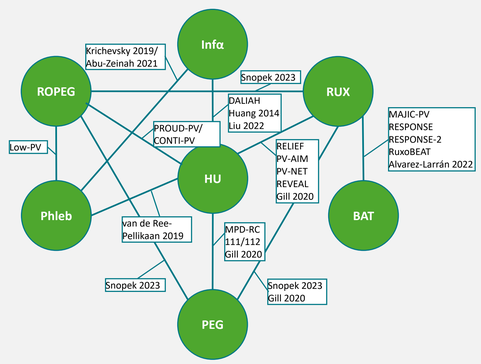
Table 1. PICOS scheme defining the inclusion criteria

Category	Inclusion criteria
Population	Patients diagnosed with Polycythemia vera
Interventions/Comparators	Ropeginterferon alfa-2b
Comparators	Peginterferon alfa-2a, Ruxolitinib, standard of care (e.g., Hydroxyurea)
Outcomes	Complete hematological response, Molecular response, Allele burden, Any adverse event, (Thrombo-) Cytopenia
Study types	Randomized controlled trials (RCTs) and comparative RW studies
Language	English
Search timeframe	May 2014 to May 2024
Bibliographic Database	PubMed
Grey literature	American Society of Clinical Oncology, American Society of Hematology, European Hematology Association

RESULTS

- A total of 193 PubMed records and 460 conference abstracts were screened, with 41 studies meeting the inclusion criteria.[4-44]
- These included 11 randomized controlled trials and 10 observational studies, providing comparative evidence for various treatment regimens in PV.
- Among the 22 studies included for the feasibility assessment, 21 formed a connected network (**Figure 1**). The study by Podoltsev 2018[38] did not provide a connection to the other studies of interest and thus was removed from the network. This study compared a mix of HU and Phleb vs. no treatment.
- Availability of complete hematological response (CHR), molecular response, allele burden and event-free survival across studies is presented in **Table 2**.

Figure 1. Best case evidence network for comparison of PV treatments for the outcomes of interest



BAT: best available therapy (HU, Infα, PEG, pipobroman, anagrelide, immunomodulators, no medication), HU: hydroxyurea, INFα: interferon-α, PEG: pegylated INFα, Phleb: phlebotomy, ROPEG: ropegylated INFα, RUX: ruxolitinib

RESULTS (continued)

Table 2. Availability of outcomes across included studies

Study	Comparison	Follow-up (months)	CHR[a]	Molecular response[f]	Allele burden[m]	Event-free survival
PROUD-/CONTINUATION-PV[11-17,21,22]	ROPEG vs. HU	Up to 72	✓[b]	✓[g]	✓	✓[o]
Low-PV[6-8]	ROPEG vs. Phleb	Up to 24		✓[h]	✓	
MPD-111/112[31-32,44]	PEG vs. HU	Up to 36	✓		✓[n]	✓[p]
DALIAH[25-27]	INFα vs. HU	36	✓	✓[i]	✓	
Huang 2014[20]	INFα vs. HU	Up to 60	✓[c]	✓[j]		✓[q]
Liu 2022[30]	INFα vs. HU	Up to 60	✓[d]	✓[h]	✓	✓[r]
Krichevsky 2019[29], Abu-Zeinah 2021[4]	INFα vs. HU vs. Phleb	Up to 336				✓[s]
van de Ree-Pellikaan 2019[40]	Phleb vs. HU vs. Phleb+HU	Up to 12	✓[d]			
Snopek 2023[39]	ROPEG vs. PEG vs. RUX	15				
RELIEF[33]	RUX vs. HU	4				
REVEAL[9]	RUX vs. HU	Up to 12				
Gill 2020[10]	RUX vs. PEG vs. HU	6	✓			
RESPONSE/ RESPONSE-2[18,23-24,34,36-37,41-42]	RUX vs. BAT	Up to 8	✓[d]	✓[k]	✓	
MAJIC-PV[19]	RUX vs. BAT	12	✓[e]	✓[l]	✓	✓[s]
PV-AIM[43]	RUX vs. HU	Up to 156				
RuxoBEAT[28]	RUX vs. BAT	6	✓			
Alvarez-Larrán 2022[5]	RUX vs. BAT	96				✓[t]

[a] For CHR, each of the following must hold: HC<45% w/o phlebotomy, Platelet count 400×10^9 /L, WBC counts10×10^9/L, normal spleen size on imaging, no disease-related symptoms (microvascular disturbances, pruritus, headache). [b] CHR without the spleen-size and/or symptoms requirements are also available. [c] CHR definition without phlebotomy requirement. [d] CHR definition without phlebotomy, spleen-size and symptoms requirements. [e] CHR definition without symptoms requirements. [f] Molecular response is defined as complete response (i.e., reduction of any molecular abnormality to undetectable levels) or partial response, applying only to patients with a baseline value of mutant allele burden ≥10% (i.e., reduction of ≥ 50% from baseline value in patients with < 50% mutant allele burden at baseline OR reduction of ≥ 25% from baseline value in patients with > 50% mutant allele burden at baseline). [g] Complete or partial response. [h] Partial response only, applying only to patients with a baseline value of mutant allele burden ≥20%. [i] Partial response only. [j] Complete or partial response without restriction on baseline allele burden. [k] Complete response only, and partial response only, applying only to patients with a baseline value of mutant allele burden ≥20%. [l] Partial response only without restriction on baseline allele burden. [m] Allele burden is provided as change from baseline. [n] Provided as medians over time. [o] Events included thromboembolic event, myelofibrosis, acute leukemia, death or disease progression, death and thromboembolic events. [p] Events included major thrombotic event, major hemorrhagic complications, myelofibrosis, acute leukemia or death. [q] Events included thrombosis, bleeding, spleen enlargement, severe myelofibrosis or death. [r] Myelofibrosis-free survival and thrombosis-free survival were reported. [s] Myelofibrosis-free survival was reported. [t] Events included major thrombosis, major hemorrhage, transformation, or death.

- Definitions of endpoints varied considerably across studies, impeding comparisons across studies. E.g.,
  - CHR rarely included requirements on spleen size and/or disease-related symptoms, and hematocrit (HC) < 45% was not always required to be reached without phlebotomy.
  - Also, molecular response was defined differently across studies, and some studies reported partial instead of complete response.
- Time points of assessment and follow-up times differed across studies, and standard of care (BAT) was differently defined, e.g., 100% HU or a mix of HU and other therapies, further precluding NMA.
- Patient populations included in the studies forming networks were heterogenous with respect to important treatment effect modifiers, including individuals newly diagnosed or untreated, with high-risk features or low-risk PV, or refractory or intolerant to HU, thus violating the homogeneity requirement of NMA (**Table 3**).

Table 3. Patient baseline characteristics of studies forming networks

Study	Study population	Arm	Age, median (IQR) [years]	Sex, M [%]	Spleen size median (IQR) [cm]	Allele burden at baseline, mean (SD) [%]
PROUD-PV[16]	Adults with PV	ROPEG	60 (52, 66)	46	13.1 (11, 15)	41.9 (24)
		HU	60 (48, 67)	47	13 (11.5, 15.2)	42.8 (24)
CONTINUATION-PV[16]	Adults with PV	ROPEG	58 (50, 64)	49	13.5 (11.5, 15)	42.8 (23)
		HU/BAT	59 (49, 65.5)	47	12.8 (11.3, 15.5)	42.9 (23)
Low-PV[7]	Low-risk patients with PV	ROPEG	51.7 (45.5, 55.3)	73.4	2.0 (2.0, 3.0)[‖]	34 (18, 57)[§,#]
		Phleb	48.2 (43.7, 57.4)	61.9	2.5 (2.0, 5.0)[‖]	27 (19, 66)[§,#]
MAJIC-PV[19]	Patients resistant/ intolerant to HU	RUX	67 (34, 88)[†]	60	14 (9, 26)[†]	64[‡]
		HU/BAT	66 (28, 85)[†]	56	14 (9, 30)[†]	58[‡]
Liu 2022[30]	PV patients	IFNα -2b	51 (44, 57)	39	NR	56 (35, 73)[§]
		HU	61 (52, 67)	49	NR	59 (33, 73)[§]
MPD-RC 112[31,*]	High-risk ET/PV patients	PEG	60 (19, 79)[†]	60	12.5 (6.5, 22)	34.5 (22.0)**
		HU	63 (18, 87)[†]	56	12.5 (2.1, 20)	36.0 (18.3)**
DALIAH[27,*]	Newly diagnosed or untreated MPN patients	IFNα	59 (20, 88)[†]	54	NR	33 (19, 51)
		HU	68 (60, 80)[†]	63	NR	37 (17, 52)
RESPONSE[41]	Patients with PV, phlebotomy-dependent patients with splenomegaly	RUX	62 (34, 90)	60	7 (0, 24)[†]	76.2 (17.8)
		BAT	60 (33, 84)	71.4	7 (0, 25)[†]	75 (22.6)
RESPONSE-2[36,37]	Adults with PV, no palpable splenomegaly, and HU resistance or intolerance	RUX	63 (54, 61)	53	NR	53 (9, 95)[†]
		BAT	67 (61, 74)	63	NR	74 (13, 95)[†]
Van de Ree-Pellikaan 2019[40]	Patients with low- and high-profile risk of PV	Phleb	58.7 (13.1)[¶]	37	NR	NR
		HU	69.1 (9.2)[¶]	12	NR	NR

ET: essential thrombocythemia; IQR: interquartile range; M: males; MPN: Myeloproliferative neoplasms, PreMF: prefibrotic myelofibrosis, PMF: primary myelofibrosis, SD: standard deviation. Note: Allele burden at baseline refers to JAK2V617F. *Baseline characteristics reported involve both PV and ET, as presented in the original publication, if not stated differently. †Median (range), ‡ Median, § Median (IQR), ‖ measured below the costal margin, ¶ Mean (SD), # Patients responding at Month 12, ** For PV patients.

LIMITATIONS

- Only comparative studies were included in the current assessment. Non-comparative studies could provide additional data that could potentially be used in unanchored comparison.

CONCLUSION

- NMA for a rare disease like PV was not feasible to conclude due to heterogeneity among studies including the population of interest, treatments, outcome definitions, length of follow-up and potential treatment effect modifiers. Population-adjusted indirect comparison methods can reduce some of the heterogeneity but require access to patient-level data.
- These published findings are valuable to share during rare disease formulary evaluations utilizing NMA to assess comparative clinical evidence when head-to-head clinical trial data is absent.

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Abbreviations: BAT: best available therapy, CHR: complete hematological response, ET: essential thrombocythemia, HC: hematocrit, HU: hydroxyurea, INFα: interferon-α, IQR: interquartile range, M: male, MPN: Myeloproliferative neoplasms, NMA: network meta-analysis, PEG: pegylated INFα, Phleb: phlebotomy, PreMF: prefibrotic myelofibrosis, PMF: primary myelofibrosis, PV: polycythemia vera, ROPEG: ropegylated INFα, RUX: ruxolitinib, SD: standard deviation, WBC: white blood cell.

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