A REAL-WORLD COMPARATIVE EFFECTIVENESS ANALYSIS OF FOSTAMATINIB VS. THROMBOPOIETIC RECEPTOR AGONISTS (TPOs) FOR TREATMENT OF CHRONIC IMMUNE THROMBOCYTOPENIA IN ADULT PATIENTS

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BACKGROUND

- Chronic immune thrombocytopenic purpura (ITP) is an acquired autoimmune disease characterized by antibody-induced platelet (PLT) destruction, leading to a reduction in the number of circulating PLTs.
- Initial treatment is with corticosteroids. In patients who become resistant/intolerant to corticosteroids, the TPOs, consisting of eltrombopag (ELT), romiplostim (ROM), and avatrombopag (AVA) or the spleen tyrosine kinase inhibitor fostamatinib (FOS), are appropriate next lines of therapy.
- In this study, the comparative safety and effectiveness between FOS and the TPOs was evaluated in a real-world community hematology setting.

METHODS

- The QCCA network database was reviewed for ITP patients who had received treatment between June 1, 2018 and December 31, 2021.
- The primary endpoints were the proportion of patients with PLT levels ≥ 30 and ≥ 50 x 10^3/µL and the proportion whose PLT levels increased by at least 2-fold relative to baseline at 3 and 6 months, respectively.
- Secondary endpoints were the use of rescue therapy for PLT related events, the development of thromboembolic events (TEs) and all reported adverse events (AEs).
- Data collection consisted of patient demographics, disease characteristics, duration of ITP, comorbidities, number and type of prior ITP treatments and PLT count prior to the start of FOS or the TPOs.
- From the first day until the end of treatment, data were collected on hemoglobin, white blood cells, absolute neutrophil counts, PLT counts, concomitant ITP therapies and the use of rescue IVIG, PLT transfusions or corticosteroids.
- The primary clinical endpoints between FOS and the TPOs were evaluated using multivariate logistic regression analysis, adjusted for clustering on the patient.
- A patient level economic analysis was also conducted.

RESULTS

- The final sample of 51, 87, 127 and 44 patients who received FOS, ELT, ROM and AVA respectively.
- Patient groups were reasonably balanced in terms of performance status, comorbidity score, hematology and biochemistry parameters at the start of therapy and median duration of ITP (Table 1).
- The fostamatinib group tended to be more heavily pretreated, with the median number of prior therapies being three, compared to two in the TPO groups (Table 2).
- AEs associated with drug discontinuations occurred in 7.8% of fostamatinib patients compared to 14.9%, 4.7% and 11.4% in the ELT, ROM and AVA groups respectively (Table 3).
- Thromboembolic events (TEs) occurred in 3.9% of fostamatinib patients compared to 9.2%, 4.7% and 11.4% in the ELT, ROM and AVA groups.
- In the 51 fostamatinib patients, there were 15 patients with PLT events (29.4%) that required active intervention. In the TPO groups, PLT related events occurred in 13.8% (n=12), 18.1% (n=23) and 13.6% (n=6) of patients treated with ELT, ROM and AVA respectively (Table 4).
- Over 12 months of continuous therapy, responding patients who remained on ELT or AVA tended to have numerically higher PLT levels than fostamatinib (Figures 1, 2).
- At month three and six, there were no meaningful differences between FOS and the TPOs in terms of the proportion of patients with the PLT count being ≥ 30 x 10^3/µL, ≥ 50 x 10^3/µL, as well as the proportion whose PLTs levels doubled relative to baseline (Figures 3, 4).
- The mean cost per patient with fostamatinib was $99,209 compared to $92,341, $108,482 and $131,050 for ELT, ROM or AVA, respectively.

RESULTS

Table 1. Demographic and clinical characteristics of patients treated with fostamatinib and TPOs.

Parameter (mean, SD)	Fostamatinib (n = 51)	Eltrombopag (n=87)	Romiplostim (n=127)	Avatrombopag (n=44)
Median age [range]	59 [21-88]	65 [21-87]	70 [21-88]	64 [25-83]
Mean weight in lbs	176 (60)	203 (67)	198 (59)	198 (60)
Female sex	68.6% (35)	54.0% (47)	56.7% (72)	54.6% (24)
ECOG Performance Status				
0 or 1	70.6% (36)	72.4% (63)	63.8% (81)	77.3% (34)
2	9.8% (5)	8.0% (7)	16.5% (21)	6.8% (3)
3	2.0% (1)	4.6% (4)	1.6% (2)	0.0% (0)
Not documented	17.6% (9)	14.9% (13)	18.1% (23)	15.9% (7)
Median duration of ITP in yrs. [range]	4.5 [1-21]	4.2 [1-26]	3.8 [1-26]	3.6 [1-23]
Prior splenectomy	39.2% (20)	12.6% (11)	24.4% (31)	20.4% (9)
Median Charlson score [range][1]	1 [0-9]	1 [0-9]	1 [0-11]	1 [0-6]
Other comorbidities				
Hypertension	41.2% (21)	67.8% (59)	45.7% (58)	43.2% (19)
Depression	15.7% (8)	16.1% (14)	15.0% (19)	15.9% (7)
Lupus	3.9% (2)	3.4% (3)	2.4% (3)	2.3% (1)
AIHA	3.9% (2)	1.1% (1)	3.9% (5)	6.8% (3)
RA	3.9% (2)	4.6% (4)	1.6% (2)	2.3% (1)
Obesity	2.0% (1)	3.4% (3)	3.1% (4)	0.0% (0)
Evans syndrome	2.0% (1)	0.0% (0)	0.0% (0)	2.3% (1)
Baseline hematology/biochemistry				
Platelets [10^3/µL]	35.2 (42.8)	35.6 (40.5)	41.4 (43.9)	40.4 (40.6)
Hemoglobin [g/dL]	12.2 (2.09)	12.6 (1.86)	12.1 (2.12)	12.4 (2.32)
White blood cells [10^3/µL]	7.01 (3.24)	6.88 (3.65)	6.13 (3.33)	6.50 (2.75)
Absolute neutrophil count [10^3/µL]	4.20 (2.02)	4.21 (3.04)	3.55 (2.33)	3.72 (1.71)
Serum creatinine [mg/dL]	1.08 (1.34)	1.45 (2.07)	0.97 (0.59)	1.45 (2.63)
ALT (IU/L)	23.1 (15.4)	31.0 (22.0)	26.9 (20.1)	23.8 (11.2)
AST (IU/L)	23.4 (14.2)	35.7 (33.2)	32.9 (23.7)	32.7 (28.8)
ALP (IU/L)	83.4 (29.1)	98.0 (68.6)	89.5 (51.6)	97.4 (64.2)

Abbreviations: AIHA = Autoimmune hemolytic anemia, ECOG: Eastern Oncology Cooperative Group
[1]The weighted comorbidity classes were: Low = 0 points, Median = 1 to 2, High = 3 to 4 and Very high = ≥ 5.

Table 2. Characteristics of prior and current ITP therapies.

Parameter	Fostamatinib (n = 51)	Eltrombopag (n=87)	Romiplostim (n=127)	Avatrombopag (n=44)
Median number of prior therapies [range]	3 [2-6]	2 [2-6]	2 [2-6]	2 [2-6]
Prior ITP therapies received				
Corticosteroids[1,2]	100% (51)	100% (87)	100% (127)	100% (44)
Romiplostim	92.1% (47)	27.5% (24)	N/A	65.9% (29)
Rituximab	70.6% (36)	44.8% (39)	52.0% (66)	38.6% (17)
Eltrombopag	60.8% (31)	N/A	37.0% (47)	38.6% (17)
IVIG	64.7% (33)	49.4% (43)	55.9% (71)	45.4% (20)
Avatrombopag	27.4% (14)	33.3% (29)	21.2% (27)	N/A
Immunosuppressants	15.7% (8)	2.3% (2)	4.7% (6)	4.5% (2)
Other[3]	39.2% (20)	26.4% (23)	22.8% (29)	47.7% (21)
Starting dose (median)	100 mg BID	50 mg QD	3 mcg/kg/wk	20 mg QD
Final dose (median)	150 mg BID	25 mg QD	5 mcg/kg/wk	20 mg QD
Duration of therapy (months)				
Mean (95%CI)	7.3 (4.3-10.3)	8.9 (6.5-11.2)	8.5 (6.6-10.4)	11.2 (7.0-15.5)
Median (IQR)	2.6 (1.5-10.0)	5.0 (0.9-14.6)	5.0 (1-12)	6.3 (1.3-21.9)
Platelet level at the start of therapy (10^3/µL)				
Mean (95%CI)	35 (21-49)	36 (25-46)	41 (32-51)	40 (24-56)
Median (IQR)	21 (4-46)	25 (10-42)	30 (12-47)	36 (9-63)
Reason for discontinuation				
Change in therapy[4]	27.4% (14)	18.4% (16)	12.6% (16)	13.6% (6)
Physician choice	9.8% (5)	13.8% (12)	20.5% (26)	6.8% (3)
Adverse event	7.8% (4)	14.9% (13)	4.7% (6)	11.4% (5)
Patient wish	2.0% (1)	4.6% (4)	3.9% (5)	4.5% (2)
Patient death	2.0% (1)	1.1% (1)	3.2% (4)	2.3% (1)
Other	7.8% (4)	9.2% (13)	17.3% (22)	11.4% (5)
Not documented	43.1% (22)	32.2% (28)	37.8% (48)	50.0% (22)

Abbreviations: IQR = interquartile range, BID = twice daily, QD = once per day, N/A = not applicable
[1]Consists of dexamethasone, prednisone and methylprednisolone.
[2]Patients were retreated with the same agents on multiple occasions, but that therapy was quantified only once.
[3]Consists of multiple agents such as dapsone, danazol, cyclophosphamide, methotrexate, anti-D, platelet transfusions and clinical trial.
[4]There were several reasons that led to a change in therapy such as decreasing efficacy, splenectomy and insurance no longer providing drug coverage.

Table 3. Adverse events during fostamatinib and TPO therapy.

Parameter	Fostamatinib (n = 51)	Eltrombopag (n=87)	Romiplostim (n=127)	Avatrombopag (n=44)
AEs reported during therapy	90.2% (46)	31.0% (27)	41.7% (53)	54.5% (24)
AEs associated with drug discontinuation	7.8% (4)	14.9% (13)	4.7% (6)	11.4% (5)
AEs leading to unplanned clinic visit	2.0% (1)	2.3% (2)	0.8% (1)	4.5% (2)
				0.0% (0)
AEs leading to ER visit	4.0% (2)	1.1% (1)	4.7% (6)	
AEs leading to hospital visit	9.8% (5)	2.3% (2)	6.3% (8)	0.0% (0)
Type of AE				
Diarrhea	17.6% (9)	4.6% (4)	2.4% (3)	0.0% (0)
Fatigue	11.8% (6)	6.9% (6)	10.2% (13)	11.4% (5)
Headache	9.8% (5)	2.3% (2)	4.7% (6)	9.1% (4)
Nausea	9.8% (5)	2.3% (2)	3.1% (4)	6.8% (3)
Hypertension	7.8% (4)	0.0% (0)	0.0% (0)	0.0% (0)
Abdominal pain	3.9% (2)	1.1% (1)	3.1% (4)	0.0% (0)
Rash	2.0% (1)	1.1% (1)	3.1% (4)	4.5% (2)
Chest pain	2.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Neutropenia	2.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Other[1]	23.5% (12)	12.6% (11)	15.0% (19)	22.7% (10)
Thromboembolic events	3.9% (2)	9.2% (8)	4.7% (6)	11.4% (5)

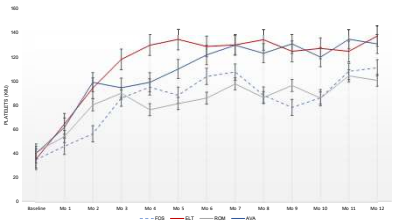
Abbreviations: AEs = adverse events, ER = emergency room
[1]These include transaminitis, hematuria, muscle aches, constipation, fluid retention, leg swelling, loss of taste, pancytopenia, dizziness, edema and vomiting.

Table 4. Platelet related events requiring rescue therapy.

Parameter	Fostamatinib (n = 51)	Eltrombopag (n=87)	Romiplostim (n=127)	Avatrombopag (n=44)
Platelet related events[1]	29.4% (15)	13.8% (12)	18.1% (23)	13.6% (6)
IVIG used as rescue therapy	15.7% (8)	9.2% (8)	8.7% (11)	9.1% (4)
IVIG dosage				
30 grams x one dose	6	0	0	0
45 grams x one dose	0	1	0	0
30 grams x two doses[2]	2	0	0	0
80 grams x one dose	0	6	9	3
80 grams x two doses[2]	2	1	2	1
Total IVIG delivered (grams)	620	685	880	400
Mean IVIG volume per patient	77.5 grams	85.6 grams	80 grams	100 grams
Platelets used as rescue therapy	25.5% (13)	11.5% (10)	12.6% (16)	18.2% (8)
Where were the platelets delivered				
ER	15.4% (2)	30.0% (3)	12.5% (2)	12.5% (1)
Clinic	0.0% (0)	0.0% (0)	6.25% (1)	0.0% (0)
Hospital	69.2% (9)	60.0% (6)	62.5% (10)	75.0% (6)
Not documented	15.4% (2)	10.0% (1)	18.8% (3)	12.5% (1)
Total units administered	18	12	23	10
Corticosteroids used as rescue therapy[3]	15.7% (8)	8.0% (7)	7.9% (10)	9.1% (4)
Median duration of corticosteroids	3 days	2 days	4 days	2 days

Abbreviations: ER = emergency room, IVIG = intravenous immune globulin
[1]Events were managed with IVIG, platelets, corticosteroids or a combination of.
[2]Administered to the same patient for the same event, so counted as one platelet event requiring IVIG.
[3]Consisted of dexamethasone, prednisone and methylprednisolone.

Figure 1. Mean platelet levels (± SE) over 12 months of therapy*.



*Note, over the 12-month period, patients who discontinued therapy were removed from the original sample.

Table 5. Thromboembolic events during therapy.

Parameter	Fostamatinib (n = 51)	Eltrombopag (n=87)	Romiplostim (n=127)	Avatrombopag (n=44)
Number of events	3.9% (2)	9.2% (8)	4.7% (6)	11.4% (5)
Type of event				
DVT	1	6	3	3
Pulmonary embolism	0	0	3	1
Superficial thrombophlebitis	1	0	0	0
Ischemic stroke	0	1	0	0
Not documented	0	1	0	1
ER visit	1	5	3	3
Hospital admission	1	6	4	5
Number of hospital days	Not documented	33	27	4
How managed				
Apixaban	1	4	1	1
Rivaroxaban	0	1	2	2
Warfarin	0	1	2	0
LMWH	0	5	3	2
Other	0	1	0	0

Abbreviations: ER = emergency room, LMWH = low molecular weight heparins

Table 6. Clinical outcomes data over 3 and 6 months of therapy.

Parameter	Fostamatinib (n = 51)	Eltrombopag (n=87)	Romiplostim (n=127)	Avatrombopag (n=44)
Response Outcomes at 3 mon				
Response 30[1]				
PLT counts < 30 x 10^3/µL	47.0% (24)	54.0% (47)	58.3% (74)	56.8% (25)
Undocumented or therapy duration < 3 mon	19.6% (10)	11.5% (10)	11.0% (14)	20.4% (9)
	33.3% (17)	34.5% (30)	30.7% (39)	22.7% (10)
Response 50[2]				
PLT counts < 50 x 10^3/µL	37.2% (19)	47.1% (41)	40.9% (52)	52.3% (23)
Undocumented or therapy duration < 3 mon	29.4% (15)	18.4% (16)	28.3% (36)	25.0% (11)
	33.3% (17)	34.5% (30)	30.7% (39)	22.7% (10)
Doubling of PLTs at 3 mon				
Yes	25.5% (13)	31.0% (27)	23.6% (30)	31.8% (14)
No	27.4% (14)	17.2% (15)	26.8% (34)	22.7% (10)
Undocumented or therapy duration < 3 mon	47.0% (24)	51.7% (45)	49.6% (63)	45.4% (20)
Response Outcomes at 6 mon				
Response 30[3]	35.3% (18)	41.4% (36)	42.5% (54)	52.3% (23)
PLT counts < 30 x 10^3/µL	5.9% (3)	4.6% (4)	11.0% (14)	6.8% (3)
Undocumented or therapy duration < 6 mon	58.8% (30)	54.0% (47)	46.4% (59)	40.9% (18)
Response 50[4]	29.4% (15)	36.8% (32)	35.4% (45)	47.7% (21)
PLT counts < 50 x 10^3/µL	11.8% (6)	9.2% (8)	18.1% (23)	11.4% (5)
Undocumented or therapy duration < 6 mon	58.8% (30)	54.0% (47)	46.4% (59)	40.9% (18)
Doubling of PLTs at 6 mon				
Yes	21.6% (11)	23.0% (20)	22.0% (28)	25.0% (11)
No	11.8% (6)	13.8% (12)	16.5% (21)	20.4% (9)
Undocumented or therapy duration < 6 mon	66.7% (34)	63.2% (55)	61.4% (78)	54.5% (24)

Abbreviations: TPOs = thrombopoietic receptor agonists
[1]Defined as patients who had a platelet level ≥ 30 x 10^3/µL at 3 months.
[2]Defined as patients who had a platelet level ≥ 50 x 10^3/µL at 3 months.
[3]Defined as patients who had a platelet level ≥ 30 x 10^3/µL at 6 months.
[4]Defined as patients who had a platelet level ≥ 50 x 10^3/µL at 6 months.

Figure 2. Box plot of platelet levels over 12 months of therapy by drug (medians and interquartile range).

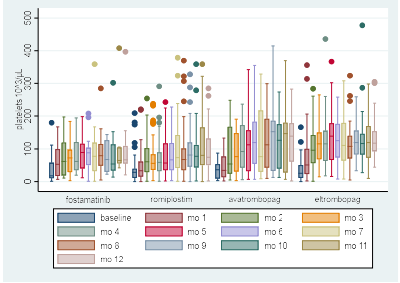
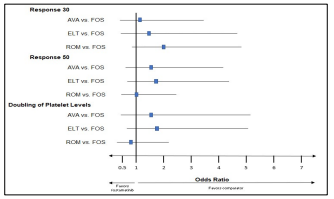
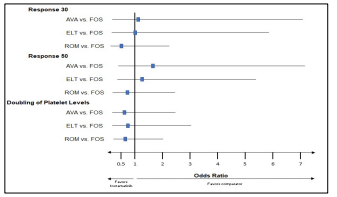


Figure 3. Forest plot of clinical outcomes at 3 months*.



*In all comparative analyses, the p value was at least > 0.13.

Figure 4. Forest plot of clinical outcomes at 6 mon*.



*In all comparative analyses, the p value was at least > 0.34.

LIMITATIONS

- This was not a prospective study, and some data was undocumented for several important parameters.
- The study was retrospective, so it was difficult to quantify the severity of bleeding events.
- This was not a randomized trial, so there was imbalance in some patient parameters at baseline.
- The study was not powered to detect significant differences in overall safety, and PLT related event endpoints.

CONCLUSIONS

- To our knowledge, a real-world comparative analysis evaluating treatment effectiveness, patient safety and resource use between fostamatinib and the TPOs has not been undertaken.
- Fostamatinib was comparable to the TPOs in maintaining platelet levels at clinically beneficial levels.
- The total cost of therapy with fostamatinib was numerically lower than that with AVA and ROM.
- Fostamatinib appeared to have a favorable side effect profile, with fewer patients with AE related treatment discontinuations and TEs requiring ER visits and hospitalizations.
- Given these findings, treatment selection should be based on overall patient safety, preexisting risk factors for TEs and cost effectiveness.

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