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Treating Anemic Patients With Myelofibrosis in the New Janus Kinase Inhibitor Era: Current Evidence and Real-world Implications

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Anemia is a prevalent and burdensome clinical manifestation of myelofibrosis (MF) with a complex etiology. Most MF patients are anemic within 1 year of diagnosis, and nearly all become dependent on red blood cell transfusions over time.[1] Anemia is associated with a reduced health-related quality of life (HRQoL) and shortened survival.[2] Moreover, anemia and transfusion dependence are independent negative prognostic indicators incorporated into standard clinical MF risk scoring systems.[3] While specific subsets of patients with MF may derive temporary anemia benefit from androgens (eg, danazol), corticosteroids (eg, prednisone), immunomodulators (eg, pomalidomide), or erythropoiesis-stimulating agents, the vast majority of patients will not achieve a prolonged response.[2] The Janus kinase inhibitor (JAKi) ruxolitinib has been a decade-long standard of care for patients with intermediate- and high-risk MF due to its efficacy in reducing spleen size and improving disease-related symptoms; however, ruxolitinib is myelosuppressive and associated with dose-dependent worsening of anemia.[4] More recently, the JAKi fedratinib and pacritinib have each been approved for the treatment of MF, having demonstrated spleen and symptom improvements compared with placebo or best available therapy.[5,6] Like ruxolitinib, new-onset or worsening anemia is commonly reported with fedratinib treatment,[5] whereas pacritinib is relatively nonmyelosuppressive.[6] Notably, the investigational agent momelotinib is the first and only JAKi to also target the iron regulator activin A receptor type 1/activin receptor-like kinase-2 (ACVR1/ALK2), addressing the unmet need of anemia in MF patients in addition to the traditional treatment goals of JAK inhibition: reducing splenomegaly and symptom burden.[2]

Due to the lack of comparative information among these expanding treatment options, a systematic literature review and network meta-analysis (NMA) of 7 randomized controlled trials of JAKi in patients with MF (noted in **Table 1**) by Sureau et al evaluated the relative efficacy and tolerability of treatments, including endpoints of reduced spleen volume and adverse events due to hematologic toxicity, among others.[7] This NMA demonstrated that ruxolitinib, momelotinib, and fedratinib were comparably efficacious in reducing spleen volume (with ruxolitinib and momelotinib providing significant improvements in achieving ≥35% spleen volume reduction at 24 weeks compared with pacritinib), while momelotinib was associated with significantly less grade 3/4 anemia compared with ruxolitinib, fedratinib, or pacritinib.[7] However, this analysis did not include real-world studies, examine anemia-related benefits among treatments (such as decreased transfusion need), or evaluate the differential impact of therapies on the HRQoL and economic burden associated with anemia and transfusions in MF.

To address this, we conducted an expanded targeted literature review within the MEDLINE, Embase, Cochrane, NHS Economic Evaluation, and Health Technology Assessment databases to identify articles published between January 2011 and February 2021 reporting treatment outcomes of phase 2 and phase 3 clinical trials and real-world studies in MF in the United States, United Kingdom, France, Germany, Italy, or Spain, with at least 25 patients per arm or cohort. Both approved (ie, ruxolitinib, fedratinib, pacritinib) and investigational (ie, momelotinib, as well as the telomerase inhibitor imetelstat and the transforming growth factor beta trap luspatercept) MF treatments were assessed. A total of 52 publications were identified, including 29 real-world studies and 23 records covering 16 clinical trials (**Table 1**). No published study of luspatercept met the inclusion criteria.

A detailed review of the 15 clinical trial publications that reported anemia- or transfusion-related outcomes in MF confirmed that momelotinib not only had the lowest grade 3/4 anemia rates among JAKi but also showed the greatest improvement in transfusion independence rates (**Table 1**). Specifically, reported rates of treatment-emergent grade 3/4 anemia ranged from 6% to 14% for momelotinib, 20% to 42% for ruxolitinib, 38% to 60% for fedratinib, 7% to 27% for pacritinib, and 30% for imetelstat. Overall, the proportion of transfusion-independent patients from baseline to week 24 or end of the treatment period decreased by 13% to 21% for ruxolitinib, decreased by 9% for fedratinib, remained stable with a 1% increase for

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HemaSphere (2022) 6:10(e778).
http://dx.doi.org/10.1097/HS9.0000000000000778.
Received: July 14, 2022 / Accepted: August 19, 2022

Table 1

Summary of the Impact of JAKi and Imetelstat on Transfusion Burden in Clinical and Real-world Studies of MF

				Anemia Rate		Impact on Transfusion Burden		
Treatment	**Publication**	**Trial name/Data Source**	**Number of Patients**	**Measurement**	**Results**	**Measurement**	**Results**	**Overall Change in %TI Patients From BL to W24 or End of Treatment**
Phase 3 clinical trials								
Ruxolitinib	Verstovsek et al. *N Engl J Med.* 2012;366:799–807.	COMFORT-1*	Ruxolitinib (n = 155) Placebo (n = 154)	Proportion of patients with grade 3 anemia during month 0–6	26.4% (ruxolitinib) 10.7% (placebo)	Proportion of patients who were TD at baseline who achieved TI during the study	41.2% (ruxolitinib) vs 46.9% (placebo) *P* = NR	NR
				Proportion of patients with grade 4 anemia during month 0–6	11.5% (ruxolitinib) 3.1% (placebo)			
	Harrison et al. *N Engl J Med.* 2012;366:787–798.	COMFORT-2*	Ruxolitinib (n = 146) BAT (n = 73)	Exposure-adjusted rate (event per 100 patient-years) of grade 3/4 anemia	21 (12.3) (ruxolitinib) 5 (7.5) (BAT)	Proportion of patients who received ≥1 RBC transfusion during the treatment period	51% (ruxolitinib) vs 38% (BAT) *P* = NR	NR
	Al-Ali et al. *haematologica* 2016; 101:1065.	JUMP	Ruxolitinib (n = 1144)	Proportion of patients with grade 3/4 anemia	33.0%	NR	NR	NR
Fedratinib	Pardanani et al. *JAMA Oncol.* 2015;1:643–651.	JAKARTA-1*	Fedratinib 400 mg daily (n = 96) Fedratinib 500 mg daily(n = 97) Placebo (n = 96)	Proportion of patients with grade 3/4 anemia	43% (fedratinib 400 mg) 60% (fedratinib 500 mg) 25% (placebo)	Proportion of patients who were TD at baseline who achieved TI during follow-up	92.3% (fedratinib 400 mg and 500 mg pooled) vs 50% (placebo) *P* = NR	–9%
Pacritinib	Mesa et al. *Lancet Haematol.* 2017;4:e225–e236.	PERSIST-1*	Pacritinib 400 mg (n = 220) BAT excluding JAKi (n = 107)	Proportion of patients with grade 3/4 anemia through W24	17% (pacritinib 400 mg) 15% (BAT)	Proportion of patients who were TD at baseline who achieved TI during follow-up	25% (pacritinib 400 mg) vs 0% (BAT) *P* = 0.043	NR
	Mascarenhas et al. *JAMA Oncol.* 2018;4:652–659.	PERSIST-2*	Pacritinib 400 mg once daily (n = 75†) Pacritinib 200 mg twice daily (n = 74†) BAT (n = 72†)	Proportion of patients with grade 3/4 anemia	27% (pacritinib 400 mg) 22% (pacritinib 200 mg) 14% (placebo)	Proportion of patients not TI at baseline who had reduced transfusion burden at W24	20.5% (pacritinib 200 mg and 400 mg pooled) vs 8.6 (BAT) *P* = NR	+1.3% (pacritinib 400 mg) +1.4% (pacritinib 200 mg) 0% change (placebo)
Momelotinib	Mesa et al. *J Clin Oncol.* 2017;35:3844–3850.	SIMPLIFY-1*	Momelotinib (n = 215) Ruxolitinib (n = 217)	Proportion of patients with grade 3/4 treatment-emergent anemia	5.6% (momelotinib) 23.1% (ruxolitinib)	Proportion of patients who were TI at W24	66.5% (momelotinib) vs 49.3% (ruxolitinib) *P* < 0.001	–2% (momelotinib) –21% (ruxolitinib)
						Proportion of patients who were TD at W24	30.2% (momelotinib) vs 40.1% (ruxolitinib) *P* = 0.019	
						Median rate of transfusion (units/month)	0 (momelotinib) vs 0.4 (ruxolitinib) *P* < 0.001	
	Harrison et al. *Lancet Haematol.* 2018;5:e73–e81.	SIMPLIFY-2*	Momelotinib (n = 104) BAT (n = 52)	Proportion of patients with grade 3/4 treatment-emergent anemia	13.5% (momelotinib) 13.5% (BAT)	Proportion of patients who were TI at W24	43% (momelotinib) vs 21% (BAT) *P* = 0.0012	+12% (momelotinib) –16% (BAT)
Phase 2 clinical trials								
Ruxolitinib	Mead et al. *Br J haematol.* 2015;170:29–39.	ROBUST	Ruxolitinib (n = 48)	Proportion of patients with grade 3/4 anemia	20.8%	Proportion of patients who were TD at baseline achieved TI by the end of the study	17% (1 out of 6 evaluable patients)	NR
	Talpaz et al. *J Hematol Oncol.* 2018;11:1–0.	NCT01445769	Ruxolitinib (n = 45)	Proportion of patients with grade 3/4 treatment- emergent anemia	20.0%	Proportion of patients who were TI	66.7% (baseline) 53.3% (by the end of treatment phase)	-13%
	Talpaz et al. *J Hematol Oncol.* 2013;6:1–0.	NCT01348490	Ruxolitinib (n = 50)	Proportion of patients with grade 3/4 anemia	42.2%	Proportion of patients who required RBC transfusion	40.0% (in 12 W before baseline) 60.0% (during the treatment phase of the study)	NR

(Continued)

Table 1 (Continued)

Treatment	Publication	Trial name/Data Source	Number of Patients	Anemia Rate		Impact on Transfusion Burden		Overall Change in %TI Patients From BL to W24 or End of Treatment
				Measurement	Results	Measurement	Results	
Ruxolitinib + lenalidomide	Daver et al. *Haematologica.* 2015;100:1058.	NCT01375140	Ruxolitinib and lenalidomide (n = 31)	NR	NR	NR	NR	NR
Fedratinib	Harrison et al. *Am J Hematol.* 2020;95:594–603.	JAKARTA-2	Fedratinib 400 mg (n = 97)	Proportion of patients with grade 3/4 treatment- emergent anemia	38%	Proportion of patients who had treatment-emergent TD	8%	NR
Pacritinib	Gerds et al. *Blood adv.* 2020;4:5825–35.	PACIFICA	Pacritinib 100 mg QD(n = 52) Pacritinib 100 mg BID (n = 55) Pacritinib 200 mg BID (n = 54)	Proportion of patients with grade 3/4 anemia	9.6% (pacritinib 100 mgQD) 7.3% (pacritinib 100 mg BID) 20.4% (pacritinib 200 mg BID)	Proportion of patients with reduction in transfusion burden by 50% or greater	17.9% (pacritinib 100mgQD) 35.5% (pacritinib 100 mg BID) 14.7% (pacritinib 200 mg BID)	NR
Momelotinib	Oh et al. *Blood adv.* 2020;4:4282–91.	NCT02515630	Momelotinib (n = 41)	Proportion of patients with grade 3 or above anemia	12%	Proportion of patients achieved TI by W24	34%	+34%
Imetelstat	Tefferi et al. *N Engl J Med.* 2015 Sep 3;373:908–19.	NCT01731951	Imetelstat (n = 33)	Proportion of patients with grade 3/4 treatment- emergent anemia	30%	Proportion of patients who TD and who achieved TI	31% (4/13)	NR
Real-world studies								
NR‡	Masarova et al. *Eur J haematol.* 2018;100:257–63.	University of Texas MD IAnderson Cancer Center	Overall (n = 1,269) Patients with platelet count > 100×10^9/L (n = 948) Patients with platelet count 50–100×10^9/L (n = 178) Patients with platelet count < 50×10^9/L (n = 145)	Proportion of patients with anemia (hemoglobin < 10 g/dL) at baseline	43% (overall) 38% (patients with platelet count > 100×10^9/L) 52% (patients with platelet count 50–100×10^9/L) 68% (patients with platelet count < 50×10^9/L)	Proportion of patients with TD at baseline	26% (overall) 18% (patients with platelet count > 100×10^9/L) 38% (patients with platelet count 50–100×10^9/L) 62% (patients with platelet count < 50×10^9/L)	NR
NR‡	Masarova et al. *Leuk Res.* 2017;59:110–6.	University of Texas MD Anderson Cancer Center	PMF (n = 755) PET/MF(N = 163) PPV/MF (N = 181)	Proportion of patients with anemia (hemoglobin < 10 g/dL) at baseline	43% (PMF) 38%(PET/MF) 41% (PPV/MF)	Proportion of patients with TD at baseline	29% (PMF) 17%(PET/MF) 20% (PPV/MF)	NR
NR‡	Naqvi et al. *Leuk Lymphoma.* 2017;58:866–71.	University of Texas MD Anderson Cancer Center	PMF (n = 24) PET/MF (N = 4) PPV/MF (N = 7)	NR	NR	NR	NR	NR
All patients treated with ruxolitinib	Kuykendall et al. *Ann hematol.* 2018;97:435–41.	Lee Moffitt Cancer Center	64	Proportion of patients with anemia (hemoglobin < 10 g/dL) prior to ruxolitinib Proportion of patients with anemia (hemoglobin < 10 g/dL) post ruxolitinib	51% 70%	NR	NR	NR
NR‡	Kuykendall et al. *Clin Lymphoma Myeloma Leuk.* 2017;17:e45–53.	Lee Moffitt Cancer Center	309	Proportion of patients with anemia OR TD at baseline	55%	Proportion of patients with anemia OR TD at baseline	55%	NR
All patients treated with ruxolitinib	Gerds et al. *ASCO Ann meeting.* 2020; e19539–e19539.	Chart review	104	NR	NR	NR	NR	NR

(Continued)

Table 1 (Continued)

Treatment	Publication	Trial name/Data Source	Number of Patients	Anemia Rate		Impact on Transfusion Burden		Overall Change in %TI Patients From BL to W24 or End of Treatment
				Measurement	Results	Measurement	Results	
NR‡	Vallapureddy et al. *Blood Cancer J.* 2019;9:1–8.	Mayo Clinic	1,306	Proportion of patients with moderate/severe anemia at first referral	54%	Proportion of patients with TD at first referral	32%	NR
NR‡	Szuber et al. *Am J Hematol.* 2018;93:1474–84	Mayo Clinic	PMF, age ≤ 40(n = 63) PMF, age 41–60 (n = 388) PMF, age >60 (n = 831)	Proportion of patients with anemia (hemoglobin < 10 g/dL) at first referral	47% (all PMFpatients) 23% (PMF, age ≤ 40) 37% (PMF, age 41–60) 54% (PMF, age >60)	Proportion of patients with TD at first referral	13% (PMF,age ≤ 40) 24% (PMF, age 41–60) 38% (PMF, age >60)	NR
NR‡	Pardanani et al. *Am J Hematol.* 2013;88:312–6.	Mayo Clinic	203	Proportion of patients with anemia (hemoglobin < 10 g/dL) at first referral	59%	Proportion of patients with TD at first referral	38%	NR
NR‡	Tefferi et al. *Mayo Clin Proc.* 2012;Vol. 87, No. 1, pp. 25–33	Mayo Clinic	1,000	Proportion of patients with anemia (hemoglobin < 10 g/dL) at first referral	54%	Proportion of patients with TD at first referral	38%	NR
All patients treated with ruxolitinib	Mascarenhas et al. *J Med Econ.* 2020;23:721–7.	Optum, MarketScan, and SEER	290	Proportion of patients with anemia	36% (30 days after ruxolitinib initiation) 53% (60 days after ruxolitinib initiation) 60% (90 days after ruxolitinib initiation) 66% (180 days after ruxolitinib initiation) 53% (30 days after ruxolitinib discontinuation) 65% (60 days after ruxolitinibdiscontinuation) 69% (90 days after ruxolitinib discontinuation) 77% (180 days after ruxolitinib discontinuation)	NR	NR	NR
NR‡	Vekeman et al. *Leuk Lymphoma.* 2015;56:2803–11.	MarketScan and IMS PharMetrics	TD patients with iron chelation therapy (n = 103) TD patients with iron chelation therapy (n = 468)	Proportion of patients with anemia	86.4% (TD patients with iron chelation therapy) 77.4% (TD patients with iron chelation therapy)	Months from first MF diagnosis to TD, median (range):	2.9 (0.03, 33.80) (TD patients with iron chelation therapy) 4.3 (0.03, 60.23) (TD patients with iron chelation therapy)	NR
NR‡	Yang et al. *ASCO Ann meeting.* 2016;e18556–e18556.	Marketscan	1,658	NR	NR	Proportion of patients with RBC transfusion by line of therapy	13% (no therapy) 25% (first-line therapy) 32% (second-line therapy) 35% (third-line therapy)	NR
All patients treated with ruxolitinib	Pemmaraju et al. *ASCO Ann meeting.* 2020;e19535–e19535.	Cardinal Health (chart review)	26	NR	NR	NR	NR	NR

(Continued)

Table 1 (Continued)

Treatment	Publication	Trial name/Data Source	Number of Patients	Anemia Rate		Impact on Transfusion Burden		
				Measurement	Results	Measurement	Results	Overall Change in %TI Patients From BL to W24 or End of Treatment
NR‡	Gimenez et al. *J Med Econ.* 2014;17:435–41.	Three hospitals in Spain	33	NR	NR	Proportion of patients who needed transfusion	*Among splenomegaly symptomatic patients:* 33% (patients with constitutional symptoms and anemia) 0% (patients with constitutional symptoms without anemia) 21% (patients without constitutional symptoms with anemia) 0% (patients without constitutional symptoms and anemia) *Among splenomegaly asymptomatic patients:* 16% (patients with constitutional symptoms and anemia) 2% (patients with constitutional symptoms without anemia) 32% (patients without constitutional symptoms with anemia) 0% (patients without constitutional symptoms and anemia)	NR
NR‡	Pastor-Galan et al. *Med Clin.* 2020;155:152–8.	Spanish Registry of Myelofibrosis (GEMMIE-2014-01)	1,000	Proportion of patients with anemia	36%	NR	NR	NR
All patients treated with ruxolitinib	Palandri et al. *Hematol Oncol.*202;38:372–80.	European Hematology centers	589	NR	NR	NR	NR	NR
All patients treated with ruxolitinib	Breccia et al. *Ann Hematol.* 2019;98:889–96.	European Hematology centers	462	Proportion of patients with ruxolitinib inducted anemia	76% (any grade, any time) 67% (any grade, at month 3) 53% (any grade, at month 3)	NR	NR	NR
All patients treated with ruxolitinib	Palandri et al. *Br J Haematol.* 2018;183:35–46.	European Hematology centers	291	Proportion of patients developed anemia of any grade during ruxolitinib therapy	93 3%	NR	NR	NR
All patients treated with ruxolitinib	Palandri et al. *Oncotarget.* 2017;8:79073.	European Hematology centers	408	NR	NR	NR	NR	NR
All patients treated with ruxolitinib	Palandri et al. *Cancer.* 2020;126:1243–52.	European Hematology centers	268	Proportion of patients with anemia (hemoglobin <10 g/dL)	51.5% (at the start of ruxolitinib) 69.9% (at discontinuation of ruxolitinib)	NR	NR	NR

(Continued)

Table 1 (Continued)

Treatment	Publication	Trial name/Data Source	Number of Patients	Anemia Rate		Impact on Transfusion Burden		Overall Change in %TI Patients From BL to W24 or End of Treatment
				Measurement	Results	Measurement	Results	
All patients treated with ruxolitinib	Palandri et al. *Hematol Oncol.* 2018 Feb;36:285–90.	European Hematology centers	70	Proportion of patients with ruxolitinib-induced anemia	45.7%	Proportion of patients requiring occasional transfusion support Proportion of patients acquired TD during ruxolitinib treatment	21.4% 4.3%	NR
All patients treated with ruxolitinib	Mazza et al. *Leuk Lymphoma.* 2017;58:138–44.	Six institutions from the Apulia region in the south of Italy	65	Proportion of patients with mild anemia during ruxolitinib treatment	5%	Proportion of patients who needed RBC transfusion	23% (before ruxolitinib) 37% (during ruxolitinib) 15% (after ruxolitinib)	NR
All patients treated with ruxolitinib	Breccia et al.*Ann Hematol.* 2019;98:1933–6.	Nine Italian hematological centers	53	Proportion of patients with grade 2 or above anemia during ruxolitinib treatment	45%	NR	NR	NR
All patients treated with ruxolitinib	Breccia et al.*Ann. Hematol.* 2017;96:387–91.	Nine Italian hematological centers	98	Proportion of patients experienced anemia of any grade	39.7%	NR	NR	NR
NR‡	Guglielmelli et al. *Am J Hematol.* 2016;91:918–922.	Six Italian centers of the AGIMM consortium	490	Proportion of patients with anemia stratified by fibrosis grade	28.0% (overall) 17.2% (grade 1 fibrosis) 29.1% (grade 2 fibrosis) 43.0% (grade 3 fibrosis)	NR	NR	NR
NR‡	Caocci et al. *Int J Hematol.* 2020;111:614–8.	One Italian medical center	106	NR	NR	Median number of RBC units received	24 (TD patients with infection complication) 15 (TD patients without infection complication)	NR
NR‡	Beauverd et al. *Br J Haematol.* 2016;175:37–42.	Guy's and St Thomas' NHS Foundation Trust (UK)	43	Proportion of patients with anemia (hemoglobin < 10 g/dL) at referral Proportion of patients who developed anemia during follow-up	7.5% 17.6%	Proportion of patients with TD at referral	7%	NR
All patients treated with ruxolitinib	Barraco et al. *Br J Haematol.* 2020;191:764–74.	The PASS (post-authorization safety study) study	259	Treatment-emergent anemia per 100 patient-years	3.8	NR	NR	NR

*Randomized controlled trial included in network meta-analysis by Sureau et al.[7]

†Only patients who completed at least 22 weeks of follow-up after randomization and before clinical hold were considered.

‡Treatment information was not extracted for real-world studies where patients used various types of treatment or where treatment use was not reported.

BAT = best available therapy; BID = twice per day; BL = baseline; JAKi = Janus kinase inhibitor; MF = myelofibrosis; NR = not reported; PET = postessential thrombocythemia; PMF = primary myelofibrosis; PPV = postpolycythemia vera; QD = once per day; RBC = red blood cell; TD = transfusion dependent; TI = transfusion independent; UK = United Kingdom; W = week.

Table 2

Summary of the Impact of Anemia on Overall Survival in Clinical and Real-world Studies of MF

Publication	Study Description	Treatment	Anemia Rate	Hazard Ratio of Anemia vs Nonanemia (95% CI), *P*	
				Univariate Analysis	Multivariate Analysis
Guglielmelli et al. *Am J Hematol.* 2016;91:918–922.	This study used 490 PMF patients with fibrosis grade ≥ 1 from 6 Italian centers of the AGIMM consortium to analyze the prognostic impact of fibrosis grade. Prognostic impacts of other clinical, hematological, and molecular variables were also reported.	NR	28%	3.28 (2.39–4.49), $P < 0.0001$	1.89 (1.33–2.70), $P < 0.0001$
Masarova et al. *Leuk Res.* 2017;59:110–116.	This study used 1,099 patients with PMF, PET/MF, or PPV/MF who were referred to the University of Texas MD Anderson Cancer Center between 1984 and 2013 to assess and compare the biologic, clinical, and prognostic features of PMF, PET/MF, and PPV/MF patients.	Hydroxyurea, ruxolitinib, stem cell transplantation, no treatment, investigational treatment, etc.	43% (PMF) 41% (PET/MF) 38% (PPV/MF)	*PMF:* 1.2 (1.02–1.5), $P = 0.03$ *PET/MF:* 1.9 (1.19–3.10), $P = 0.007$ *PPV/MF:* 1.75 (1.17–2.63), $P = 0.007$	*PMF:* 1.27 (1.02–1.58), $P = 0.031$ *PET/MF:* Not statistically significant *PPV/MF:* 1.81 (1.17–2.78), $P = 0.008$
Palandri et al. *Cancer.* 2020;126:1243–1252.	This study investigated 268 patients who discontinued ruxolitinib between June 2011 to October 2018 from a multicenter (consisting of 20 European hematology centers) observational retrospective study. The study investigated reasons for discontinuation and impact on outcomes (e.g., overall survival).	Ruxolitinib	69.9% after discontinuation of ruxolitinib	1.70 (1.05–2.76), $P = 0.03$	1.92 (1.19–3.11), $P = 0.01$
Szuber et al. *Am J Hematol.* 2018;93:1474–1484.	This study investigated 3,023 patients with myelofibrosis who were seen at MayoClinic between 1967 and 2017. The study assessed the natural history, prognostic markers, and long-term outcomes among these patients.	NR	47%	2.6 (0.84–7.2), $P = 0.09$	NR
Tefferi et al. *Mayo Clin Proc.* 2012;87:25–33.	This study assessed 1,000 patients with PMF who were seen at Mayo Clinic between 1977 and 2011. This study (1) reported clinical and laboratory features for both patients seen at time of diagnosis and those seen at different time points from diagnosis, (2) presented the natural history of the disease, including overall and leukemia-free survival, in the context of contemporary prognostic scoring systems, and (3) assessed the prognostic impact of relevant risk factors.	Allogeneic stem cell transplant, ruxolitinib, pomalidomide, etc.	54%	2.4 (2.1–2.9), $P < 0.001$	1.6 (1.3–2.1), $P < 0.001$
Verstovsek et al. *J Hematol Oncol.* 2017;10:156.	This study analyzed the long-term survival in patients treated with ruxolitinib for myelofibrosis using the 5-year data pooled from the COMFORT 1 and COMFORT II trials.	Ruxolitinib or placebo (COMFORT I) Ruxolitinib or BAT (COMFORT II)	45.8% (ruxolitinib) 49.8% (control)	*Ruxolitinib arm:* 2.70 (1.64, 4.44) *Placebo arm:* 1.51 (0.92, 2.34)	NR

BAT = best available therapy; CI = confidence interval; MF = myelofibrosis; NR = not reported; PET = postessential thrombocythemia; PMF = primary myelofibrosis; PPV = postpolycythemia vera.

pacritinib, and ranged from a 2% decrease to a 12% increase for momelotinib. Notably, momelotinib-treated patients experienced a higher rate of transfusion independence at week 24 compared with those treated with ruxolitinib in the head-to-head phase 3 SIMPLIFY-1 trial (66.5% versus 49.3%, nominal $P < 0.001$) and those treated with best available therapy (88.5% ruxolitinib) in SIMPLIFY-2 (43% versus 21%, nominal $P = 0.0012$).[8,9] Further, momelotinib-treated patients experienced lower rates of transfusion dependence at week 24 than ruxolitinib-treated patients in SIMPLIFY-1 (30.2% versus 40.1%, nominal $P = 0.019$), where the median rate of transfusion was 0 units/month with momelotinib compared with 0.4 units/months with ruxolitinib (nominal $P < 0.001$).[8]

Our targeted literature review also identified a growing body of real-world evidence demonstrating the substantial clinical burden associated with anemia and transfusions among patients with MF. Specifically, we identified 29 real-world reports of anemia- and transfusion-related outcomes (**Table 1**), including 14 studies conducted in the US (9 single-center studies, 3 database analyses, and 2 chart reviews), 14 conducted in Europe (11 multicenter, 2 single-center, and 1 registry study), and 1 conducted globally (multicenter registry study). Rates of anemia and transfusion dependence varied widely across the 24 real-world studies that directly reported it; among these MF populations, 5% to 93.3% of patients were anemic and 7% to 62% were transfusion dependent. Reported rates of ruxolitinib treatment modification due to anemia ranged from 8% to 36%, and rates of ruxolitinib discontinuation due to anemia ranged from 5% to 33%.

Additionally, we identified 5 real-world studies and 1 pooled clinical trial analysis that evaluated the association between anemia and overall survival in patients with MF, which include a range of treatments (**Table 2**). Among these, 5 of the 6 studies demonstrated an association between anemia and shortened overall survival (univariate hazard ratio range: 1.20–3.28; multivariate hazard ratio range: 1.27–1.92), and a similar trend was observed in the sixth study (**Table 2**), consistent with the known negative prognostic value of anemia in MF.[3]

Although the substantial clinical burden associated with anemia and transfusion dependence has been well documented in patients with MF, our review sought to quantify the impact of anemia and transfusions on HRQoL and economic outcomes in this specific patient population. Overall, we found that data from adequately sized MF patient populations is lacking in these areas.

An investigation from the Nordic MPN Study Group found that transfusion-dependent patients with MF had significantly worse QoL scores than nontransfusion dependent patients; however, this study did not meet our review inclusion criteria for sample size per cohort, and it did not address economic implications.[10] In patients with myelodysplastic syndromes, myeloid neoplasms with many features in common with MF including anemia, transfusion burden is associated with significant HRQoL and economic burden, with transfusion-dependent patients incurring 53% higher total costs over 2 years.[11] Future investigation is needed to quantify the full HRQoL and economic impact attributable to anemia and transfusion dependence in MF to assess the true value of current therapies as well as emerging treatments that have the potential to address all key hallmarks of MF, including anemia, splenomegaly, and symptoms.

Consistent with findings from Sureau et al,[7] our expanded targeted literature review corroborates the inadequacy of ruxolitinib in addressing the unmet need among anemic patients with MF in real-world clinical practice. Anemic MF patients receiving ruxolitinib may require dose reductions, treatment interruptions, or early treatment discontinuation, which can reduce treatment efficacy, or red blood cell transfusions throughout the course of therapy. Furthermore, nearly 50% of MF patients treated with ruxolitinib require add-on agents to treat anemia, such as androgens, corticosteroids, or erythropoiesis-stimulating agents.[12] Despite the use of supportive measures, the median duration of ruxolitinib treatment in the real-world setting is shorter than in clinical trials.[13] While the reasons for this short duration of treatment may be multifaceted, evidence suggests that adverse events (including anemia) and loss of treatment response are important contributing factors.[13]

The emergence of treatment options that directly address anemia in addition to the other key hallmarks of MF may lead to improved patient outcomes. Momelotinib inhibition of ACVR1/ALK2 in addition to JAK1 and JAK2 leads to decreased hepcidin, the master regulator of iron metabolism that is elevated in MF patients, and subsequent increased serum iron availability for erythropoiesis.[14] Momelotinib may be a valuable first- or second-line JAKi option for anemic patients with MF, as its ability to reduce rates of anemia and transfusion dependence in addition to spleen volume and symptoms has been demonstrated in phase 3 trials and further confirmed by Sureau et al.[7] In addition, several combination therapies are in advanced clinical development that have demonstrated clinical activity against anemia and other key hallmarks of MF, including ruxolitinib plus luspatercept, an activin receptor IIB ligand trap/erythroid maturation agent, ruxolitinib plus pelabresib, a bromodomain and extra-terminal protein (BET) inhibitor, and ruxolitinib plus navitoclax, a antiapoptotic B-cell lymphoma protein (BCL-X_L, BCL-2, BCL-w) inhibitor.[15] Studies to address the substantial evidence gap identified in our targeted literature review surrounding quantification of the HRQoL and economic burden of anemia and transfusions in MF will be imperative to assessing therapeutic value among the growing number of currently available and new agents entering the MF treatment landscape.

AUTHOR CONTRIBUTIONS

JS and BK designed the study. JS conducted the search. ATG, PB, GH, AK, LMN, JS, BK, and CH analyzed the data and interpreted the findings. LMN wrote and edited the manuscript with input from ATG, PB, GH, AK, JS, BK, and CH.

DISCLOSURES

Aaron T. Gerds has served as a consultant for Celgene/Bristol Myers Squibb, Pfizer, Kartos Therapeutics, Promedior, and CTI BioPharma; Prithviraj Bose has received research support from Incyte, Bristol Myers Squibb, CTI BioPharma, Constellation/Morphosys, Kartos, Blueprint Medicines, Cogent, Pfizer, Astellas, NS Pharma and Promedior, and honoraria from Incyte, Bristol Myers Squibb, CTI BioPharma, Sierra Oncology, Abbvie, Constellation/Morphosys, Karyopharm, Pharma Essentia, Blueprint Medicines and Novartis; Gabriela S. Hobbs served as a consultant for Celgene/Bristol Myers Squibb, Pfizer, Blueprint Medicines, Incyte, Novartis, Abbvie, Keros and Pharmaxis; Andrew T. Kuykendall has received clinical research funding from Sierra Oncology, Constellation/Morphosys, and Celgene/Bristol Myers Squibb and has served on advisory boards for CTI Biopharma, Novartis, Abbvie, Celgene/Bristol Myers Squibb, Constellation/Morphosys, and Imago Biosciences; Lynn M. Neilson and Barbara Klencke are employees of Sierra Oncology; Jinlin Song is an employee of Analysis Group; and Claire Harrison has received clinical research funding from Novartis, Constellation, and Bristol Myers Squibb, and has served on advisory boards and as a speaker for Novartis, Celgene/Bristol Myers Squibb, CTI BioPharma, Gilead Sciences, Shire, Roche, Janssen, Promedior, Geron, AOP, Galecto, Sierra Oncology, Constellation, and Keros, and is Deputy Editor in Chief of HemaSphere.

SOURCES OF FUNDING

Momelotinib is sponsored by Sierra Oncology. The targeted literature search was performed by Analysis Group, which was sponsored by Sierra Oncology.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

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