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REVIEW ARTICLE

VIA MEDICA

Treatment options for anaemia in myelofibrosis

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Introduction

Primary myelofibrosis (PMF) is one of the myeloproliferative neoplasms (MPN) without the BCR-ABL fusion gene [1]. This group also includes polycythemia vera (PV) and essential thrombocythemia (ET) [2]. Myelofibrosis can also result from myelofibrotic transformation of both PV and ET (when it is known as post-PV-MF, post-ET-MF) [2]. MF carries the worst prognosis among the Ph-negative MPNs, primarily due to the increased risk of transformation to acute leukaemia [1, 3]. The cause of MF remains largely unknown. The leading mutations found in most patients are mutations in the *JAK2*, *CALR* and *MPL* genes. All of these cause constant activation of the JAK-STAT signalling pathway, resulting in excessive proliferation of megakaryocytes, which secrete growth factors that stimulate the activity of fibroblasts in the bone marrow (BM) and numerous proinflammatory cytokines [4]. Myelofibrosis is usually accompanied by constitutional symptoms (including fatigue, weight loss, fever, bone pain), splenomegaly and anaemia [1]. Anaemia may result from the underlying disease (MF-related anaemia) or can be a side effect of therapy (treatment-related anaemia). Regardless of the cause, anaemia significantly worsens patients' quality of life, and in addition, MF-related anaemia is a poor prognostic factor [5–7].

Current treatment options for MF-related anaemia include erythropoiesis-stimulating agent (ESA), androgens (danazol), glucocorticoids, and immunomodulatory drugs (IMiDs). All of them are characterised by limited efficacy and durability of response, and in many cases packed red blood cells (RBCs) transfusions remain the only effective therapy [8]. In recent years, thanks to progress in the understanding of the pathogenesis of MF, many new therapies have been developed aimed not only at reducing the spleen volume and general symptoms, but also at stimulating erythropoiesis. These include new JAK inhibitors, e.g. pacritinib and momelotinib, as well as drugs with other targets such as luspatercept, imetelstat, and pelabresib. This review article discusses the pathogenesis and clinical significance of anaemia in MF and presents new treatment options.

Epidemiology of MF-related anaemia

Moderate anaemia, defined as when the haemoglobin (Hb) level is less than 10 g/dL, occurs in c.35% of MF patients, and nearly one quarter of patients require RBC transfusions [6, 9]. In Barraco et al.'s [10] study including 722 patients with PMF, as many as 87% had anaemia at diagnosis: 37% severe (Hb <8 g/dL), 16% moderate (Hb 8–10 g/dL), and almost half mild anaemia (below the gender reference range, but above 10 g/dL). In another retrospective analysis [11] including 1,109 patients, a similar rate of patients with anaemia was found, with a median Hb level at diagnosis of 10.1 g/dL (range: 5–16.7). Regardless of the severity, anaemia was significantly more common in women than in men. Moderate or severe anaemia was found more frequently in patients >65 years (56% and 65%, respectively) and with more advanced disease [11].

In patients with secondary myelofibrosis, the median Hb level at diagnosis is slightly higher (c.11 g/dL), albeit with increasingly severe anaemia over time [12]. Hb levels are lower in patients with post-ET MF than in patients with post-PV MF, and they correlate with the grade of bone marrow fibrosis [13, 14].

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Prognostic significance of anaemia

Anaemia is the main symptom of MF in addition to constitutional symptoms and splenomegaly. Its presence significantly worsens patients' quality of life, not only due to the burden of symptoms, but also because of the requirement for periodic hospitalisation to allow the RBC transfusion [15]. In today's era of JAK2 inhibitors, which significantly reduce splenomegaly-related and general symptoms, anaemia is the most important factor worsening quality of life. Additionally, anaemia affects the prognosis of patients with MF. The significance of anaemia as a prognostic factor is underlined by the fact that it is included in all prognostic scoring systems used in MF patients, both the first ones, based only on clinical data such as the International Prognostic Scoring System (IPSS) and Dynamic IPSS (DIPSS), as well as more modern ones which also take into account molecular and cytogenetic aberrations, e.g. MIPSS70 (Mutation-enhanced IPSS) and DIPSS plus [1, 6, 7, 16, 17]. In the DIPPS index, which assesses prognosis already during the course of the disease, anaemia <10 g/dL is the only factor assigned 2 points, and in the DIPPS plus index, RBC transfusions-dependence is additionally specified [6, 7].

Pathogenesis of MF-related anaemia

The pathogenesis of MF-related anaemia is very complex, with different dominant processes at different stages of the disease, and it is still not fully understood. The primary process underlying the development of anaemia is the gradual displacement of erythropoiesis from the bone marrow resulting from fibrosis [18]. This in turn leads to the activation of extramedullary haematopoiesis, among others locations in the spleen. It is currently believed that extramedullary haematopoiesis in the spleen is associated with abnormal transport of BM-derived clonal progenitor cells and stem cells as a result of dysregulation of the cytokine balance in the bone marrow [19]. Haematopoietic cells proliferate and alter splenic microarchitecture, leading to splenomegaly [20]. Haematopoiesis in the spleen is unable to provide an adequate number of erythrocytes, which results in anaemia. The enlarged spleen excessively sequesters and destroys circulating erythrocytes, contributing to increased anaemia severity [21]. Additionally, processes similar to those in anaemia in the course of chronic diseases associated with excessive expression of hepcidin, the main protein regulating iron absorption, play an important role in the development of MF-related anaemia. In MF, an increased hepcidin level results from increased secretion of inflammatory cytokines, especially interleukin 6 (IL-6) and excessive activation of the BMP6/ACVR1/SMAD (bone morphogenetic protein/activin receptor/Smad protein) pathway. Bone morphogenetic proteins are pleiotropic cytokines belonging to the transforming growth factor beta (TGFβ) superfamily. They are bound by two different types of receptors with serine-threonine kinase activity, and the second messengers of the intracellular signal are Smad proteins [22]. Pathogenic mechanisms of MF-related anaemia are presented schematically in Figure 1.

Anaemia in MF patients may also be iatrogenic and occur as a result of treatment, including JAK inhibitors or hydroxyurea (HU). In addition to the above-mentioned causes, there are also other possible factors leading to the development of anaemia in MF patients, e.g. concomitant chronic diseases, chronic blood loss (gastric/duodenal ulcer, oesophageal varices, haemolysis), and iron or vitamin deficiency. In the differential diagnosis of new-onset or worsening anaemia, causes not directly related to MF should always be considered.

Treatment of MF-related anaemia

MF-related anaemia is a therapeutic challenge. Currently, the options used in clinical practice include RBC transfusions, ESAs, androgens (danazol), glucocorticoids, and IMiDs. Their efficacy and influencing factors are set out in Table I. Due to differing patient populations and differing definitions of treatment response, direct comparisons between the clinical trials listed in Table I and assessments of the efficacy of different treatment options are not possible. For clinical trial purposes, the International Working Group for Research and Treatment of Myeloproliferative Neoplasms (IWG-MRT) and the European LeukaemiaNet have standardised the definition of transfusion dependency (TD) in MF patients: it consists of a requirement for transfusion of ≥6 RBC units within 12 weeks prior to study entry, with Hb level <8.5 g/dL, in the absence of bleeding or treatment-related anaemia, and the last transfusion coming within 28 days of study entry. Transfusion independence (TI) is classified as the absence of RBC transfusions during any 12-week treatment period (in the study) while maintaining Hb level >8.5 g/dL [23].

Erythropoiesis-stimulating agent (ESAs)

Erythropoiesis-stimulating agents activate proerythroid signalling, resulting in increased erythrocyte production. Recombinant human erythropoietin (rhEPO) and darbepoetin α are used in the treatment of MF-related anaemia. Prospective clinical trials with ESAs involved a small number of patients, and the response to treatment ranged between 20% and 45% [24, 25]. In retrospective studies, the differences in the efficacy of ESAs were even greater, and some did not prove their efficacy in any patient [26]. Predictive factors of response to ESA therapy include low baseline endogenous erythropoietin (EPO) serum activity and low transfusion requirements. However, even in patients eligible for treatment, the response rate is not predictable and patients will eventually become refractory

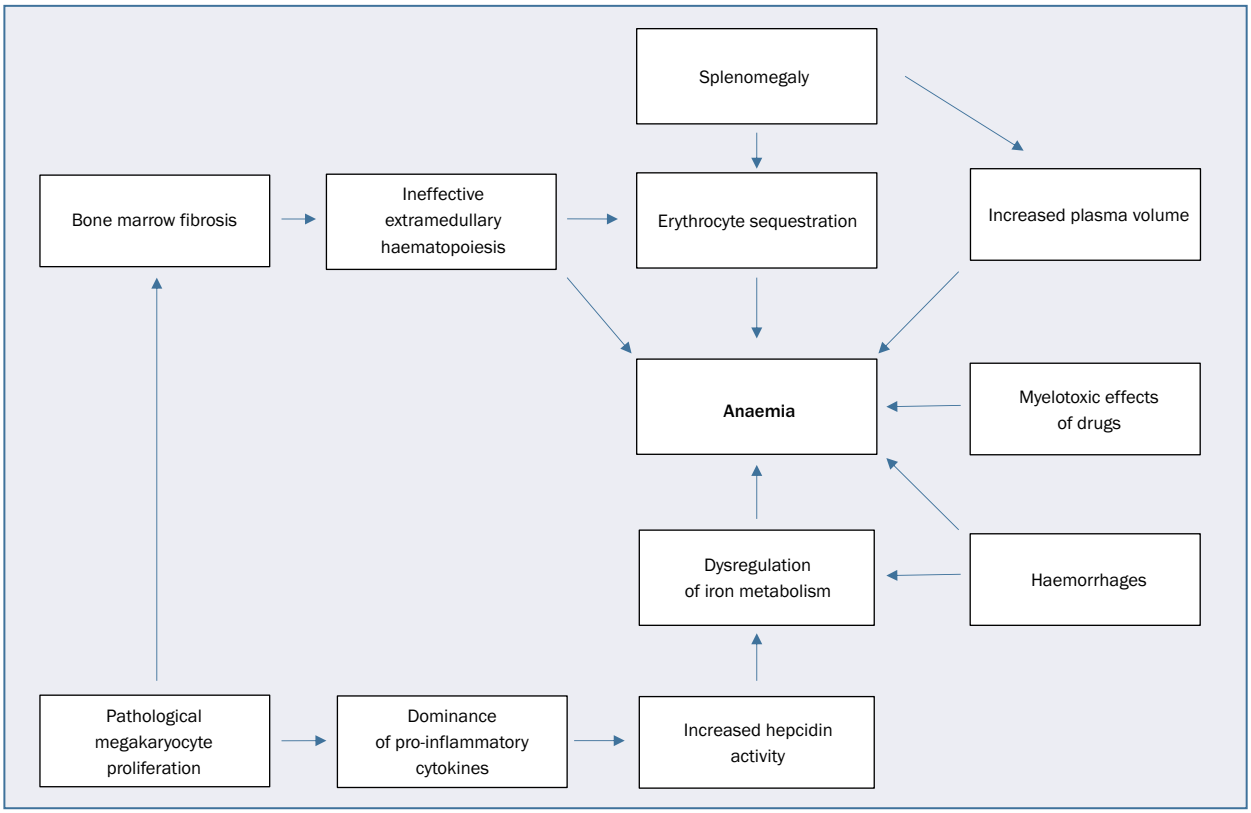

Figure 1. Causes of anaemia in myelofibrosis. Developed based on [21]

to ESA therapy [27]. The main limitations of ESA use in MF patients are thus their limited efficacy in transfusion-dependent patients, the risk of progression of splenomegaly, and thrombotic complications [1]. In Poland, EPO is not reimbursed in patients with MF.

Androgens

Androgens have erythropoiesis-stimulating properties that are used in the treatment of MF-related anaemia, although their exact mechanism of action is not fully understood [28]. Initially, testosterone enanthate and oral fluoxymesterone were used, but due to a better safety profile and tolerability, only danazol, a synthetic, attenuated androgen, is now used [29]. The recommended dose is 600 mg/day. The response rate is c.30%, including 44% in patients who are transfusions independent and 19% in transfusions-dependent patients [29]. The most common adverse effect of danazol is increased liver enzyme activity, which usually resolves after dose reduction. Danazol cannot be used in patients with androgen-dependent tumours such as prostate cancer, previous or active thrombosis, or significantly impaired liver or kidney function.

Immunomodulatory drugs (IMiDs)

The first report of the efficacy of this group of drugs concerned thalidomide, which was used in a patient with very advanced MF. The result was a significant reduction in spleen size and bone marrow fibrosis after 30 months of therapy [30]. The positive effect of IMiDs in reducing anaemia, thrombocytopenia and, to a lesser extent, splenomegaly in patients with MF results from the broad anti-inflammatory, antiangiogenic, antiproliferative and immunomodulatory effects of this group of drugs [31]. In clinical studies, IMiDs have been used either as monotherapy or in combination with glucocorticoids (see Tab. I). Small sample sizes, the addition of other drugs, as well as different inclusion criteria and ways of assessing responses make it difficult to assess their true effectiveness. In the initial studies, thalidomide was used in high doses (400–500 mg/d), which showed efficacy in reducing anaemia, but the treatment was swiftly discontinued due to high toxicity, mainly polyneuropathy. Subsequent studies have shown that doses of 50–100 mg/d allow for the maintenance of treatment response with significantly lower toxicity [32]. Studies have shown the efficacy of low-dose thalidomide in combination with prednisone in c.40% of cases, with a median duration of response (DoR) of 16 weeks [27]. In some patients, even such low doses of thalidomide (50–100 mg/d) can cause fatigue, constipation, and neuropathy.

In Mesa et al.'s [33] phase II study with lenalidomide, a second-generation IMiD, the response rate was c.20% when the drug was used as monotherapy and 30% when

Table I. Options for treating anaemia in patients with myelofibrosis

Drug/method	Study	Study population	Indications	Results	Factors influencing treatment response
ESAs	Cervantes [24]	n = 20 Median Hb 8.9 g/dL	Hb <10 g/dL or transfusion dependence	Response rate: 45%: 20% TI 25% reduction in transfusion requirements	Transfusion independence Epo activity <125 U/L
	Hernández--Boluda [25]	n = 163 Median Hb 9.3 g/dL	Hb <10 g/dL Epo <125 U/L	Response rate: 53%: 29% in TD patients, 53% in TI patients	Female gender Leukocytes >10 G/L Ferritin <200 ng/mL
Androgens (danazol)	Cervantes [29]	n = 50 Median Hb 8.5 g/dL	Hb <10 g/dL	Response rate: 30%: 19% in TD patients 44% in TI patients	
IMiDs					
Thalidomide vs. placebo	Abgrall [72]	n = 52 Median Hb 8.8 g/dL	Hb <9 g/dL or transfusion dependence	Response rate: 17% (thalidomide) vs. 16% (placebo) Reduction in transfusion requirements 16% vs. 26%	Not found Only 10 patients completed six months of treatment High treatment toxicity
Lenalidomide + + prednisone	Mesa [33]	n = 48 Median Hb 9.1 g/dL	Hb <10 g/dL or transfusion dependence	Response rate: 19%	Not found. 35% of patients did not complete treatment. High haematological toxicity.
Pomalidomide vs. placeboRESUME study	Tefferi [36]	n = 229 Median Hb 8.7 g/dL	Hb <9 g/dL or transfusion dependence	Response rate: 16% (pomalidomide) vs. 16% (placebo)	Transfusions <4 RBC units/month Age <65 Primary myelofibrosis
Splenectomy	Tefferi [39]	n = 223 Median Hb 10.4g/dL	Splenectomy for anaemia or symptomatic splenomegaly	37% in TD patients	PLT >50 G/L High cellularity of bone marrow
RBC transfusions	Elena [41]	n = 220 Median Hb 11 g/dL 14% TD (Median Hb 7.1 g/dL)	Comparison of prognosis of TD to TI patients	NA	Transfusion dependency shortens overall survival

Epo — erythropoietin; ESA — erythropoiesis stimulating factors; Hb — haemoglobin; IMiDs — immunomodulatory drugs; NA — not applicable; PLT — platelet count; RBC — red blood cells; TD — transfusion-dependent; TI — transfusion-independent

in combination with prednisone. Haematological toxicity was the main problem: the authors found the frequency of haematological toxicities to be as high as 88% despite the addition of prednisone [33]. The only comparison of thalidomide with lenalidomide to date was conducted by Jabbour et al. [34], who evaluated 125 patients treated in three consecutive phase II studies. Thalidomide was used in doses increasing up to 800 mg/d (n = 44), lenalidomide in a dose of 10 mg/d (n = 41), and lenalidomide in combination with prednisone in doses of 10 mg and 30 mg (n = 40). Lenalidomide-based therapy was more effective (34–38%) than thalidomide (16%; $p = 0.06$). The combination of lenalidomide and prednisone resulted in a significantly longer duration of response (median 34 months) compared to either lenalidomide or thalidomide monotherapy (median 7 and 13 months, respectively; $p = 0.042$) [34].

The newest drug in this group is pomalidomide, which shows the most favourable safety profile, but data on its efficacy also differs significantly. In a phase II study with 96 patients with MF-related anaemia, in which pomalidomide was used as monotherapy, 39% of patients achieved

a response to treatment, and the median duration of response was 13 months [35]. But in a phase III study with 229 patients, the response rate in the pomalidomide arm was similar to that of a placebo [36].

To conclude, IMiDs show moderate efficacy in patients with MF-related anaemia, but the main limitation of their use is toxicity. The most common adverse events are haematological toxicity, polyneuropathy, fatigue, and constipation. Currently, studies are underway to combine IMiDs with JAK2 inhibitors. Preliminary results indicate clinical benefits and moderate toxicity with sequential use of the drugs [37, 38].

Splenectomy

Treatment-refractory symptomatic splenomegaly in MF patients may be an indication for splenectomy [1]. Splenectomy leads to the resolution of symptoms related to spleen enlargement, and reduces anaemia, thrombocytopenia, and portal hypertension, but is also associated with a significant risk of complications. In a retrospective analysis from the Mayo Clinic covering 23 patients with MF and anaemia who underwent splenectomy, 37.6% of patients became RBC transfusions independent or maintained an Hb level >10 g/dL [39]. Perioperative mortality was 9%, and complications occurred in 30% of patients, most often increased platelet (PLT) count and thromboembolic or haemorrhagic episodes. The results of splenectomy were also summarised in a more recent analysis from the same centre, including 120 consecutive patients with MF who underwent splenectomy, with median age 66 and a transfusion-dependent rate of 60% [40]. During a median post-splenectomy follow-up of 1.3 years, 95 (79%) deaths and 30 (25%) leukaemic transformations were reported. Median overall survival (OS) after surgery was 1.5 years. Factors adversely affecting survival included age >65, RBC transfusion dependence, leukocyte count >25 G/L, and peripheral blasts (PB) ≥5% [40]. Splenectomy in MF patients is mainly performed as palliative therapy, and the complete blood count (CBC) improvement is only seen in the short term. The procedure is associated with a high risk of perioperative complications, including fatal ones.

Packed red blood cells (PRBCs) transfusion

Red blood cells transfusion dependence is very common in patients with advanced MF, and its occurrence is associated with a significant reduction in overall survival [9, 41]. Complications of RBC transfusion include alloimmunisation and iron overload. Due to the expected short-term survival associated with transfusion dependence, iron chelation is usually not used unless the patient is considered a candidate for allogeneic haematopoietic stem cell transplantation (ASCT) [1]. With this in mind, one goal of MF therapy should be to maximise the time window during which the patient does not require RBC transfusions.

JAK2 inhibitor therapy and anaemia

JAK inhibitors have significantly changed the therapy landscape for patients with MF. Their use allows for reductions of general symptoms and spleen size, as well as OS prolongation [1]. Unfortunately, due to JAK-STAT pathway inhibition, which is their primary mechanism of action, they also inhibit normal haematopoiesis, which may result in new-onset or worsening of anaemia or thrombocytopenia [42]. Such results are exerted primarily by the first two registered JAK inhibitors: ruxolitinib (RUX) and fedratinib (FED). The next two, pacritinib and especially momelotinib, inhibit erythropoiesis to a much lesser extent, and improve red blood cell parameters in a significant percentage of patients due to their additional mechanisms of action. A summary of the results of pivotal studies of JAK inhibitors, including the response in terms of anaemia, is set out in Table II.

Ruxolitinib

Ruxolitinib was the first JAK inhibitor approved for the treatment of MF patients [43]. The approval was based on the results of the COMFORT I and COMFORT II studies [44, 45]. COMFORT I compared RUX to a placebo in the treatment of 309 patients with IPSS intermediate-2 or high-risk MF. The dose of RUX ranged from 15 to 20 mg depending on the baseline PLT count. The primary endpoint of this study was spleen volume reduction of at least 35% (SVR35) after 24 weeks of treatment. In the RUX arm, the endpoint was met by 41.9% of patients, compared to just 0.7% in the placebo arm (p <0.0001). Additionally, 45.9% of patients had at least a 50% reduction in the total syndrome score (TSS50) [44]. The COMFORT-II study involved 219 patients in intermediate-2 and high-risk groups and compared RUX to best available therapy (BAT) [45]. The primary endpoint was the same as in COMFORT-I. After 24 weeks of treatment, 32% of patients treated with RUX achieved SVR35, compared to zero patients in the BAT arm. After 48 weeks of treatment, patients receiving RUX had significant reductions in MF-related symptoms, including loss of appetite, dyspnoea, fatigue, insomnia, and pain, whereas these symptoms worsened in patients receiving best available therapy. Assessment of constitutional symptoms and quality of life measures in this study were based on the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life questionnaire core model) and FACT-Lym (Functional Assessment of Cancer Therapy–Lymphoma) scales [45].

In a 3-year pooled analysis of data from both studies, patients treated with RUX had a longer OS [46]. This was also true for patients who transferred to the RUX arm during the course of the study. In both studies, anaemia and thrombocytopenia were the most common adverse events, albeit

Table II. JAK inhibitors approved for treatment of MF

Drug	Target	Study	Population	Treatment	SVR35 at week 24	TSS50	Response in terms of anaemia	Toxicity
Ruxolitinib (RUX)	JAK1 JAK2	COMFORT-1 phase III [44]	309 MF patients Int-2 or high risk	15–20 mg BID (depending on PLT count) vs. placebo	41.9% vs. 0.7%	45.9% vs. 5.3 %	TI: 41% (14/34 TD)	Grade 3/4 anaemia: (COMFORT-1: 45.2%, COMFORT-2: 42%), Thrombocytopenia Headache Opportunistic infections
		COMFORT-2 phase III [45]	219 MF patients Int-2 or high risk	15–20 mg BID (depending on PLT count) vs. BAT	32% vs. 0%	NA	NA	
Fedratinib (FED)	JAK1 JAK2 JAK3 TYK3	JAKARTA phase III [51]	289 MF patients Int-2 or high risk	400 mg/d vs. 500 mg/d vs. placebo	36% vs. 40% vs. 1%	36% vs. 34% vs. 7%	TI: 88% (7/8 TD)	Grade 3/4 anaemia: FED 400: 43% FED 500: 60% Placebo: 25% JAKARTA-2: 38%. Increased transaminase, lipase and amylase activity. Wernicke's encephalopathy
		JAKARTA-2 phase II [52]	97 MF patients Int-1 with symptoms, int-2 or high risk RUX resistance/ /intolerance	400 mg/d	30%	27%	NA	
		FREEDOM [53]	38 MF patients Int or high risk according to DIPSS RUX resistance/ /intolerance	400 mg/d	9%	16%	NA	Grade 3/4 anaemia: 36.9% Grade 3/4 thrombocytopenia: 23.7% Grade 3 infections: 15.8%
		FREEDOM2 [54]	201 MF patients Int-2 or high risk RUX resistance/ /intolerance	400 mg/d vs. BAT	36% vs. 6%	NA	NA	Grade 3/4 anaemia: 9%. Grade 3/4 thrombocytopenia: 12%
Pacritinib (PAC)	JAK2 ACVR1 IRAK1 FLT3 CSF1R	PERSIST-1 phase III [73]	327 MF patients Int-1, int-2 or high risk JAK inhibitor naïve vs. BAT (excluding RUX)	400 mg/d	19%	19%	TI: 25% (9/36 TD)	Thrombocytopenia Anaemia Diarrhoea Fluid retention Heart failure Squamous cell carcinoma of skin
		PERSIST-2 [61]	311 MF patients Int-1, int-2 or high risk Regardless of JAK inhibitor exposure PLT count <100 G/L vs. BAT (including 45% with RUX)	400 mg/d or 200 mg BID	18%	25%	TI ≥8 weeks Hb increase ≥2 g/dL: 25% (11/44 with Hb <10 g/ /dL)	

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Table II. (cont.) JAK inhibitors approved for treatment of MF

Drug	Target	Study	Population	Treatment	SVR35 at week 24	TSS50	Response in terms of anaemia	Toxicity
Momelotinib	JAK1 JAK2 ACVR1	SIMPLIFY-1 [57]	432 MF patients Int-1 with symptoms, int-2 or high risk PLT count ≥50 G/L JAK inhibitor naïve vs. RUX	200 mg/d	26.5%	28.4%	TI: 66.5%	Anaemia Thrombocytopenia Neutropenia Increased transaminase, lipase and amylase activity. Peripheral polyneuropathy 1st dose effect (transient hypotension, flushing, nausea, dizziness)
		SIMPLIFY-2 phase III [58]	156 MF patients Int-1 with symptoms, int-2 or high risk RUX resistance/ /intolerance vs. BAT (including 89% with RUX)	200 mg/d	7%	26.2%	TI: 43%	
		MOMENTUM phase III [59]	195 MF patients Int-1, int-2 or high risk with symptoms PLT count ≥25 G/L Hb <10 g/dL Prior treatment with JAK inhibitor vs. danazol	200 mg/d	23%	25%	TI: 31%	

ACVR1 — activin A receptor type I; BAT — best available therapy; BID — twice daily; CSF1R — colony stimulating factor 1 receptor; DIPSS — Dynamic International Prognostic Scoring System; FED — fedratinib; Hb — haemoglobin; int-1 — intermediate risk-1; int-2 — intermediate risk-2; IRAK1 — interleukin-1 receptor-associated kinase 1; JAK — Janus kinase; MF — myelofibrosis; NA — not applicable; PAC — pacritinib; PLT — platelets; RUX — ruxolitinib; SVR35 — reduction in spleen size by ≥35%; TD — transfusion dependent; TI — transfusion independent; TSS50 — 50% reduction in severity of symptoms on TSS (total syndrome score); TYK — tyrosine kinase

with a low discontinuation rate [44, 45]. In the COMFORT I study, grade ≥3 anaemia occurred in 45.2% of patients in the RUX arm compared to 19.2% in the placebo arm [44]. The frequency of this complication in the COMFORT II study was similar in the RUX arm (42%) but higher in the BAT arm (31%) [45]. Gupta et al. [47] conducted a post-hoc analysis of both COMFORT studies to determine the long-term effects of anaemia caused by RUX treatment. This analysis showed that 61% of patients who did not have anaemia at baseline developed it during the treatment, while 69% of patients with anaemia at baseline experienced its worsening. In both cases, anaemia did not adversely affect OS [47]. The nadir of Hb level was observed after 8–12 weeks of treatment, after which Hb level returned to close to baseline values [44, 45, 47]. Nevertheless, anaemia during RUX treatment is a significant clinical challenge. In real-world studies, it has been the reason for RUX therapy discontinuation in c.10% of patients [48]. RUX-related anaemia has been successfully managed with ESA or a dose reduction below that based on PLT count [49, 50].

The phase II REALIZE study evaluated the efficacy and safety of a new strategy of ruxolitinib dosing featuring a reduced starting dose and delayed dose escalation in patients with MF-related anaemia. The primary endpoint was the proportion of patients achieving ≥50% reduction in spleen size at week 24. Secondary endpoints included anaemia and transfusion requirements, safety, and assessment of constitutional symptoms. The study included 51 MF patients with splenomegaly on physical examination and a haemoglobin level <10 g/dL. During the first 12 weeks, patients received 10 mg RUX twice daily, regardless of their baseline PLT count. In patients with stable PLT counts >100 G/L and without 50% reduction in spleen length, the dose was increased to 15 mg. In the absence of splenic response, the dose was increased by 5 mg every four weeks up to a maximum dose of 25 mg if the PLT count was >200 G/L. By weeks 24 and 48, 26.2% and 32.4% of patients, respectively, had received a total daily dose of RUX ≥30 mg. At study end, 12.0% of patients maintained the increased doses and 30.0% maintained the initial dose. The great majority of patients continuously receiving the initial dose achieved a splenic response at week 12 or later (11/15 patients). Median Hb levels remained stable throughout the study period, with no increase in transfusion requirements. Platelet counts and Hb levels were similar in patients who received an increased dose compared

to those in whom the dose had not increased during the study. The results of this study support the efficacy of lower doses of RUX in reducing spleen size and constitutional symptoms without significantly worsening anaemia. This dosing strategy may be appropriate for MF patients with clinically significant anaemia [50].

Fedratinib

The second JAK inhibitor approved for the treatment of MF patients was fedratinib (FED). This drug was approved in 2019 based on the results of the JAKARTA and JAKARTA-2 studies, which included patients with intermediate-2 or high-risk MF according to IPSS, previously untreated with a JAK2 inhibitor (JAKARTA) or resistant/intolerant to RUX (JAKARTA-2) [51, 52]. The primary endpoint in both studies was the percentage of patients with SVR35, and the secondary endpoint was TSS50. JAKARTA included 289 patients who were randomised to one of three arms: placebo, or FED at a dose of 400 mg, or FED at a dose of 500 mg. After 24 weeks of treatment, the primary endpoint was achieved by 1%, 36% and 40% of these patients, respectively. The reduction of general symptoms differed significantly between the placebo arm (7%) and both FED arms, although the higher dose did not translate into a higher percentage of patients meeting this endpoint (36% of patients receiving 400 mg and 34% of patients receiving 500 mg). Anaemia was a significant complication of treatment and was dose-dependent: grade 3 or higher occurred in 43% of patients receiving 400 mg and in 60% of patients receiving 500 mg, whereas in the placebo arm it occurred in only 25% of patients [51]. JAKARTA-2 was a single-arm phase II study evaluating the efficacy of FED at a dose of 400 mg in intermediate-2 and high-risk patients resistant to or intolerant of RUX [52]. The study included 97 patients, 30% of whom met the primary endpoint of SVR35, and TSS50 was achieved in 26% of patients by the end of cycle 6 [52]. Grade ≥3 anaemia occurred in 38% of patients and was the most common reason for dose reduction, apart from increased serum lipase activity. In 2013, clinical trials with FED were stopped due to a suspected case of Wernicke's encephalopathy (WE), which led to premature termination of the JAKARTA-2 study.

The phase IIIb FREEDOM study evaluated the efficacy and safety of FED in patients with intermediate- or high-risk MF and platelet counts ≥50 G/L previously treated with RUX [53]. The study protocol included clear guidelines for mitigating the risk of gastrointestinal AEs, thiamine supplementation, and close monitoring for signs of encephalopathy. These actions included delaying or modifying the FED dose, prophylactic, and supportive use of antiemetics (e.g. ondansetron), supportive use of antidiarrhoeal medications, and dietary modification. Due to the COVID-19 pandemic, only 38 patients were included in the study. In the efficacy population (n = 35), nine patients achieved the primary endpoint of SVR35 at the end of cycle 6 (25.7%; 95% CI 12.5–43.3); and 22/38 (62.9%) patients showed the best overall response of SVR35 at the end of treatment. Sixteen (44.4%) patients achieved ≥50% reduction in constitutional symptoms after six cycles of treatment. Haematological AEs occurred in 28 (73.7%) patients. Grade 3/4 anaemia and thrombocytopenia were the most common AEs, occurring in 15 (39.5%) and nine (23.7%) patients, respectively. Gastrointestinal AEs were reported in 34 (89.5%) patients, most commonly grade ≤2. The most common gastrointestinal AE was constipation (50%). The incidence of diarrhoea was highest in cycle 1, and the incidence of vomiting generally decreased over time. There were no cases of grade ≥3 nausea, vomiting, or diarrhoea. Compared to the JAKARTA-2 study, the frequency of gastrointestinal AEs was lower, and no patient developed encephalopathy [53].

The FREEDOM2 study was a multicentre, open-label, randomised, controlled phase III study including patients with intermediate-2 or high-risk MF with known resistance or intolerance to RUX who received FED at a dose of 400 mg/d or BAT (randomisation 2:1) [54]. Patients received prophylactic antiemetics and thiamine supplementation, and symptomatic antidiarrhoeal medications as needed. The primary endpoint was a SVR35 rate after six months of treatment. The study included 201 patients (134 in the FED arm, 67 in the BAT arm), of whom 52 received RUX. The primary endpoint (SVR35 at six months) was achieved by 36% of patients receiving FED compared to 6% of patients receiving BAT (95% CI 20–39, p <0.0001). Grade 3 or higher adverse events occurred in 40% of patients receiving FED and 12% of patients receiving BAT. The most common adverse events were anaemia (9% in each arm) and thrombocytopenia (12% in the FED arm and 3% in the BAT arm). Gastrointestinal AEs were more common in the fedratinib arm compared to the BAT arm, but were mostly grade 1/2 [54].

Fedratinib is a treatment option for patients with intolerance to or failure of RUX therapy, allowing a splenic response to be achieved in c.33% of patients, although there is no advantage over RUX in terms of haematological toxicity.

Momelotinib

Momelotinib, another JAK kinase inhibitor, inhibits not only JAK1 and JAK2, but also the activin A receptor type I (ACVR1), reducing hepcidin levels and increasing the availability of iron used for Hb production [55]. The drug was registered by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) in 2023 for MF patients with anaemia. Phase I/II studies assessing the safety of the drug had already showed its beneficial effect on Hb levels in

patients with MF-related anaemia [56]. Reduced anaemia was observed in 45% of patients, and 52% of patients with TD at baseline achieved transfusion independence within eight weeks. The phase III SIMPLIFY-1 study compared the efficacy of momelotinib to that of RUX in 432 patients with high-risk, intermediate-2, and symptomatic intermediate-1 MF [57]. SIMPLIFY-1 was designed as a non-inferiority study with the option to transfer to momelotinib after 24 weeks. SVR35, the primary endpoint of the study, was met by similar percentages of patients in both groups: 27% and 29% of patients treated with momelotinib and RUX, respectively ($p = 0.11$). The percentage of patients achieving TSS50, the secondary endpoint, was smaller in the momelotinib arm compared to patients treated with RUX (28% vs. 42%), which resulted in a failure of noninferiority criterion meeting. However, a beneficial effect of momelotinib on red blood cell parameters was observed in this study. Transfusion independence at 24 weeks was achieved by 67% of patients in the momelotinib group and 49% of patients in the RUX group ($p < 0.001$). The median number of RBC units transfused was also lower in the momelotinib group (0 vs. 0.4, $p < 0.001$). Grade 3/4 anaemia was observed in only 5.6% of patients treated with momelotinib, but in 23% in the RUX group. Peripheral neuropathy was observed in 10% of patients in the momelotinib group and 5% in the BAT group, although it was mild in most patients [57].

Another phase III study, SIMPLIFY-2, included 156 patients previously treated with RUX who required RBC transfusions, had grade 3/4 thrombocytopenia or anaemia during therapy, or required a dose reduction of RUX [58]. Patients received momelotinib or BAT (and 89% of patients in this group were pretreated with RUX). SVR35 was achieved by only 7% of patients in the momelotinib group and 6% in the BAT group. This low response rate was probably due to the initiation of momelotinib immediately after RUX discontinuation, without a washout period. TSS50 was reported in 26% of patients treated with momelotinib and 6% of patients in the BAT group ($p = 0.0006$). A beneficial effect of momelotinib on the red blood cell system was also observed in this study. Patients in the momelotinib group required fewer RBC transfusions (median 0.5 units/month vs. 1.2 units/month, $p = 0.39$) and a higher percentage of patients achieved TI (43% vs. 21%, $p = 0.0012$). The percentage of patients who developed grade 3/4 anaemia or thrombocytopenia was similar in both groups. Peripheral neuropathy was observed in 11% of patients in the momelotinib group, compared to zero patients in the BAT group [58].

MOMENTUM is a phase III study comparing the efficacy of momelotinib and danazol in 195 MF patients previously treated with a JAK inhibitor and with an Hb level <10 g/dL [59]. In contrast to SIMPLIFY-1, a 2-week treatment-free period was required after discontinuation of JAK inhibitor therapy before initiation of momelotinib or danazol. As expected, both TSS50 (25% vs. 9%, $p = 0.0095$) and SVR35 at 24 weeks (23% vs. 3%, $p = 0.0006$) were reported more frequently in patients treated with momelotinib. Transfusion independence was achieved by 31% of patients in the momelotinib group and 20% of patients in the danazol group ($p = 0.0064$). The incidence of thrombocytopenia and neutropenia was similar in both groups [59].

Pacritinib

In a similar way to momelotinib, pacritinib inhibits ACVR1 in addition to JAK1 and JAK2 kinases, which translates into a beneficial effect on erythropoiesis. In addition, it has been proven that the drug inhibits IRAK1 (interleukin-1 receptor-associated kinase 1) [60]. The drug has been registered by the FDA for MF patients with a PLT count <50 G/L. Unfortunately, pacritinib is not available in Europe due to a lack of EMA registration. The pivotal study of pacritinib, PERSIST-2, included 311 MF patients with a platelet count <100 G/L [61]. Patients received pacritinib at a dose of 200 mg twice daily, or at a dose of 400 mg once daily, or BAT (sometimes RUX). In patients in the pacritinib groups, splenic and TSS50 responses were observed more frequently than in the BAT group. SVR35 was achieved by 18% vs. 3% of patients, respectively ($p < 0.00$) and 25% vs. 14% of patients, respectively ($p = 0.08$). An improvement in red blood cell parameters and a reduction in the number of RBC transfusions were also observed, especially in patients receiving pacritinib at a dose of 200 mg twice daily [61]. A retrospective analysis of pacritinib's efficacy in patients with platelet counts <50 G/L showed similar efficacy and tolerability of the drug [62].

In the phase III PACIFICA study (NCT03165734), currently ongoing, pacritinib is being compared to treatment of physician's choice (*i.e.* low-dose RUX, danazol, steroids, HU) in patients with advanced MF and severe thrombocytopenia [63].

New drugs inhibiting activin receptor

Luspatercept is a recombinant fusion protein consisting of the extracellular domain of activin (ActRIIB) and the Fc fragment of IgG. It has the ability to bind to transforming growth factor β2 (TGF-β2) family ligands and to inhibit the activation of the ActRIIB receptor and signalling through the Smad2/3 pathway. Inhibition of the Smad2/3 pathway restores the maturation of erythroid precursors in the late stage of erythropoiesis [64]. Luspatercept is approved for the treatment of anaemia in patients with myelodysplastic syndromes (MDS) and β-thalassemia [65–67]. The results of clinical trials also indicate drug activity in MF patients. The phase II ACE-536-MF-001 study included 95 MF patients with anaemia, assigned to one of four cohorts:

- Cohort 1: TI patients, currently not treated with a JAK inhibitor;

- Cohort 2: TD patients, currently not treated with ruxolitinib;
- Cohort 3A: TI patients, currently receiving ruxolitinib;
- Cohort 3B: TD patients, currently receiving ruxolitinib [68].

The primary endpoint of the study was the response in terms of anaemia. In TI patients, the response was defined as an increase in Hb level ≥1.5 g/dL, and in TD patients as transfusion independence for at least 12 weeks. The highest efficacy of luspatercept was observed in cohort 3B (TD patients treated with RUX), with 26% of patients becoming transfusion independent. The primary endpoint was also met by 14% of patients in cohorts 1 and 3A, and by 10% of patients in cohort 2. Half of all TD patients had at least a 50% reduction in the number of transfusions [68]. The phase III INDEPENDENCE study is currently ongoing, evaluating the efficacy of luspatercept compared to a placebo in TD patients with MF treated with RUX (NCT04717414).

Sotatercept has a similar mechanism of action, binding to ligands of the TGF-β2 family and inhibiting activation of ActRIIA receptor [69]. In a phase II study, the drug was used in MF patients with anaemia and an Hb level <10 g/dL, in 27 patients as monotherapy, and in 19 in combination with RUX. A response in terms of improvement of red blood cell parameters was observed in 30% of patients in both groups [69].

Conclusions

Anaemia remains a significant problem in the treatment of patients with MF. The emergence of new therapeutic options gives rise to the hope that it will be possible to improve red blood cell parameters in a higher percentage of patients. Newer JAK inhibitors such as pacritinib and, above all, momelotinib, additionally improve red blood cell parameters in a significant percentage of patients thanks to an additional mechanism of action based on ACVR1 inhibition, while maintaining the characteristic ability of JAK inhibitors to reduce splenomegaly and general symptoms.

Great expectations await the results of studies with luspatercept and sotatercept, drugs with the ability to bind to ligands of the TGF-β2 family as well as to inhibit the activation of the ActRII receptor and signal transduction through the Smad2/3 pathway, thereby restoring the maturation of erythroid precursors in the late stage of erythropoiesis.

Numerous new drugs with very different mechanisms of action are currently being tested in clinical trials. It is expected that their action will not be limited to reducing spleen size and general symptoms of the disease. The preliminary efficacy results of many of these drugs indicate an effect on reducing bone marrow fibrosis and the load of the mutant allele *JAK2*, *CALR*, *MPL*, as well as improving normal haematopoiesis, including red blood cell parameters. The molecules in advanced clinical trials include:

- pelabresib — an inhibitor of BET (Bromodomain and Extra-terminal) proteins;
- navetemadin — an inhibitor of HDM2 (human double-minute homologue;
- imetelstat — a telomerase inhibitor;
- navitoclax — an inhibitor of BCL-2/BCL-xL (B-Cell Lymphoma-2/extra-large);
- bomedemstat — an inhibitor of LSD1 (lysine-specific demethylase 1).

These molecules are being tested both in first line treatment (as add-on therapy to RUX) and in patients with suboptimal response or resistance to JAK inhibitors. Initial results of these studies prompt the hope that many of these new drugs will find a place in MF therapy, increasing the efficacy of JAK inhibitors and reducing their haematological toxicity [70, 71].

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The authors contributed equally to the creation of the article.

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