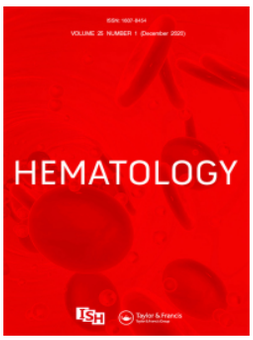

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Updated recommendations on the use of ruxolitinib for the treatment of myelofibrosis

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ABSTRACT

Objectives: Myelofibrosis is a rare bone marrow disorder associated with a high symptom burden, poor prognosis, and shortened survival. While allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment for myelofibrosis, the only approved and reimbursed pharmacotherapy for non-HSCT candidates in Belgium is ruxolitinib.

Methods: These updated recommendations are based on a consensus reached during two meetings and provide guidance for ruxolitinib administration in myelofibrosis patients considering the particularities of Belgian reimbursement criteria.

Results and Discussion: In Belgium, ruxolitinib is indicated and reimbursed for transplant-ineligible myelofibrosis patients from intermediate-2- and high-risk groups and from the intermediate-1-risk group with splenomegaly. Our recommendation is to also make ruxolitinib available in the pre-transplant setting for myelofibrosis patients with splenomegaly or heavy symptom burden. Before ruxolitinib initiation, complete blood cell counts are recommended, and the decision on the optimal dosage should be based on platelet count and clinical parameters. In anemic patients, we recommend starting doses of ruxolitinib of 10 mg twice daily for 12 weeks and we propose the use of erythropoiesis-stimulating agents in patients with endogenous erythropoietin levels $\leq$500 mU/mL. Increased vigilance for opportunistic infections and second primary malignancies is needed in ruxolitinib-treated myelofibrosis patients. Ruxolitinib treatment should be continued as long as there is clinical benefit (reduced splenomegaly or symptoms), and we recommend progressive dose tapering when stopping ruxolitinib.

Conclusion: Based on new data and clinical experience, the panel of experts discussed ruxolitinib treatment in Belgian myelofibrosis patients with a focus on dose optimization/monitoring, adverse events, and interruption/rechallenge management.

KEYWORDS
Ruxolitinib; myelofibrosis; symptom burden; splenomegaly; transplantation; anemia; reimbursement; Belgium

Introduction

Myeloproliferative neoplasms are rare bone marrow disorders characterized by clonal proliferation of hematopoietic cell lineages, which comprise polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF) [1]. MF has worse prognosis, with main causes of death including acute leukemia transformation, comorbid conditions, and consequences of cytopenia [1,2]. MF is characterized by progressive anemia, bone marrow fibrosis, and extramedullary hematopoiesis with splenomegaly, and is associated with a heavy symptom burden (e.g. night sweats, fever, bone pain, and weight loss) [2–4]. Patients can be diagnosed with primary MF, or patients with PV or ET can develop post-PV or post-ET MF [2]. MF is associated with a dysregulation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway [5]. One of the three driver mutations (Janus kinase 2 [*JAK2*], calreticulin [*CALR*], or myeloproliferative leukemia virus oncogene [*MPL*]) is found in around 90% of MF patients [2,6]. The remaining 'triple negative' MF patients have poor clinical outcomes [6]. Other high-molecular risk (HMR) mutations contributing to disease progression include *ASXL1*, *SRSF2*, *EZH2*, *IDH1*, *IDH2*, and *U2AF1* [2].

Several models estimating the prognosis and survival of MF patients were developed [2]. Two scoring systems estimated survival from time of diagnosis (international prognostic scoring system [IPSS]) [7] or any point in disease course (dynamic IPSS [DIPSS]) [8] based on five clinical risk factors alone or in combination with karyotype, platelet count, and transfusion status (DIPSS-plus [9]) (Table 1). The three more

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Table 1. Prognostic models in primary myelofibrosis.

IPSS [7]	DIPSS [8]	DIPSS-plus [9]		MIPSS70 [11]		MIPSS70+ version 2.0 [12]		GIPSS [10]
Clinical variables	Clinical variables	Clinical variables	Genetic variables	Clinical variables	Genetic variables	Clinical variables	Genetic variables	Genetic variables
Age >65 years (1)	Age >65 years (1)	Age >65 years (1)	Unfavorable karyotype (1)	Hemoglobin <10 g/dL (1)	One HMR mutation (1)	Severe anemia (2)	Very high-risk karyotype (4)	Very high-risk karyotype (2)
Hemoglobin <10 g/dL (1)	Hemoglobin <10 g/dL (2)	Hemoglobin <10 g/dL (2)		Leukocytes >25 × 10^9/L (2)	≥2 HMR mutations (2)	Moderate anemia (1)	Unfavorable karyotype (3)	Unfavorable karyotype (1)
Leukocytes >25 × 10^9/L (1)	Leukocytes >25 × 10^9/L (1)	Leukocytes >25 × 10^9/L (1)		Platelets <100 × 10^9/L (2)	Type 1/like *CALR* absent (1)	Circulating blasts ≥2% (1)	≥2 HMR mutations (3)	Type 1/like *CALR* absent *(1)*
Circulating blasts ≥1% (1)	Circulating blasts ≥1% (1)	Circulating blasts ≥1% (1)		Circulating blasts ≥2% (1)		Constitutional symptoms (2)	One HMR mutation (2)	*ASXL1* mutation (1)
Constitutional symptoms (1)	Constitutional symptoms (1)	Constitutional symptoms (1)		Constitutional symptoms (1)			Type 1/like *CALR* absent (2)	*SRSF2* mutation (1)
		Platelets <100 × 10^9/L (1)		Bone marrow fibrosis grade ≥2 (1)				*U2AF1Q157* mutation (1)
		Transfusion need (1)						

Notes: DIPSS, dynamic IPSS; GIPSS, genetically-inspired prognostic scoring system; HMR, high molecular risk; IPSS, international prognostic scoring system; MIPSS70, mutation-enhanced international prognostic scoring system for transplant-age patients; MIPSS70+, karyotype-enhanced MIPSS70. Severe anemia is defined as hemoglobin levels <8 g/dL in women and <9 g/dL in men and moderate anemia as hemoglobin levels 8–9.9 g/dL in women and 9–10.9 g/dL in men.
Risk categories based on patients' risk scores according to each prognostic system and the expected median survival for all age categories (IPSS, DIPSS and DIPSS-plus) or for patients ≤70 years of age (MIPSS70, MIPSS70+ and GIPSS):
IPSS: low (risk score, 0; median survival, 11.3 years); intermediate-1 (1; 7.9 years); intermediate-2 (2; 4.0 years); high (≥3; 2.3 years).
DIPSS: low (0; not reached); intermediate-1 (1–2; 14.2 years); intermediate-2 (3–4; 4 years); high (5–6; 1.5 year).
DIPSS-plus: low (0; 15.4 years); intermediate-1 (1; 6.5 years); intermediate-2 (2–3; 2.9 years); high (≥4; 1.3 years).
MIPSS70: low (0–1; 27.7 years); intermediate (2–4; 7.1 years); high (≥5; 2.3 years)
MIPSS70+ version 2.0: very low (0; not reached); low (1–2; 16.4 years); intermediate (3–4; 7.7 years); high (5–8; 4.1 years); very high (≥9; 1.8 years).
GIPSS: low (0; 26.4 years); intermediate-1 (1; 8.0 years); intermediate-2 (2; 4.2 years); high (≥3; 2 years).

recent prognostic models incorporated mutations, karyotype, and sex-adjusted hemoglobin (Hb) levels (mutation-enhanced IPSS for transplantation-age patients [MIPSS70], karyotype-enhanced MIPSS70 scoring system [MIPSS70+ version 2.0], and genetically-inspired prognostic scoring system [GIPSS]) [10–12]. Risk stratification and overall mutation profile characterization in MF patients are useful to guide therapeutic strategies, particularly the decision to perform allogeneic hematopoietic stem cell transplantation (HSCT).

While HSCT is the only curative MF treatment, it is not feasible in elderly patients, patients with prohibitive comorbidities, or asymptomatic patients with low-risk MF due to transplant-related mortality and morbidity [2,13]. Other treatment options for MF patients are limited and their main aim is to alleviate symptoms. In Belgium, the only pharmacotherapy with approved and reimbursed indications for MF treatment is ruxolitinib (*Jakavi*™, Novartis AG), an orally bioavailable *JAK1* and *JAK2* inhibitor [14]. In 2018, guidance on the safe and effective administration of ruxolitinib for MF treatment was published, considering the particularities of Belgian reimbursement criteria [15]. The current manuscript is based on a consensus reached by five Belgian hematologists during two meetings and is an update of these recommendations in the light of changes in Belgian reimbursement criteria, recently published data, and clinical experience.

Which patients may benefit from ruxolitinib?

Ruxolitinib can be used for the treatment of disease-related splenomegaly and symptoms in HSCT-ineligible MF patients, regardless of their *JAK2* mutational status [14]. In patients with IPSS intermediate-2-/high-risk MF, two pivotal Phase III randomized clinical trials showed that ruxolitinib is well-tolerated and induces spleen size reductions and MF-related symptom improvements compared with placebo (COMFORT-I) or best available treatment (COMFORT-II) [16,17]. After 5 years, ruxolitinib-treated patients had significantly prolonged median overall survival (OS) versus patients treated with placebo (hazard ratio [HR]: 0.69, 95% confidence interval [CI]: 0.50–0.96; p=0.025) or best available therapy (HR: 0.67, 95% CI: 0.44–1.02; p=0.06) [18,19].

In patients with intermediate-1-risk MF and palpable spleen length ≥5 cm below left costal margin (LCM), non-randomized studies showed that ruxolitinib has a safety and efficacy profile consistent with those observed in higher risk categories [20–22]. In the global JAK Inhibitor Ruxolitinib in Myelofibrosis Patients (JUMP) Phase IIIb study, >60% of 163 IPSS intermediate-1-risk MF patients with splenomegaly had ≥50% reduction in spleen length after 24 weeks and symptom improvements were observed [22]. A secondary analysis of the JUMP study and a retrospective study suggested that ruxolitinib induced higher spleen response rates in patients from lower IPSS risk categories, and when used earlier and at higher doses [23,24]. In another study, the OS probability after 5 years was higher in patients with intermediate-1-risk MF who received JAK inhibitor therapy versus HSCT (0.68 [95% CI: 0.57–0.82] versus 0.60 [0.43–0.83]), while the opposite was observed for patients with intermediate-2-risk or high-risk MF (0.37 [0.24–0.55] versus 0.45 [0.32–0.62]) [25].

In patients with low- or intermediate-1-risk MF without splenomegaly but with a high disease burden, ruxolitinib may reduce disease-related inflammation and constitutional symptoms, and improve survival and quality of life. Mutation-based scoring systems and presence of HMR mutations could be used to identify patients at increased risk for aggressive clinical course [26,27]. Besides prognosis, the presence of a high disease burden may also be considered to guide treatment strategies for patients with low- or intermediate-1-risk MF, as suggested in a recently proposed treatment algorithm [27]. However, additional studies are needed to determine whether potential benefits of early ruxolitinib given alone or in combination with other drugs outweigh potential risks and to evaluate the impact of the mutational status and disease burden in this population.

In Belgium, ruxolitinib is reimbursed for intermediate-2- and high-risk MF patients with or without splenomegaly since several years [15]. It is now also reimbursed for symptomatic intermediate-1-risk MF patients with a palpable splenomegaly ≥5 cm below LCM confirmed by imaging [28]. To be eligible for reimbursements, MF patients must have a life expectancy >6 months and must be ineligible for HSCT [28]. No definitive recommendation can be made regarding the use of ruxolitinib in patients with low- or intermediate-1-risk MF without splenomegaly, and further studies are needed to guide clinical decisions.

Ruxolitinib in the pre-transplant period

Allogeneic HSCT is the only curative treatment for transplant-eligible MIPSS70+ high-risk or very high-risk or GIPSS high-risk MF patients [2,29]. Non-randomized clinical trials and retrospective studies suggested that pre-HSCT ruxolitinib treatment is well-tolerated and may improve post-transplant outcomes and survival [30–32]. Responders to ruxolitinib seemed to have better post-HSCT outcomes than non-responders [31], which could be due to a more favorable biology of ruxolitinib-treated patients or to ruxolitinib-induced amelioration of their clinical status (decreased splenomegaly and constitutional symptoms). Of note,

while ruxolitinib can be used as bridge to HSCT, transplant-eligible candidates should not be selected based on their response to ruxolitinib but rather on criteria such as their age, major comorbidities, clinical and genetic prognostic variables, psychosocial status, preference, and caregiver availability [2,29]. There is currently no consensus concerning the best timing to perform HSCT in patients responding well to ruxolitinib. European guidelines for primary MF recommend initiation of ruxolitinib ≥2 months before transplantation, careful weaning 5–7 days before conditioning, and complete withdrawal on the day before conditioning [33]. Some reports show that abrupt discontinuation of ruxolitinib before conditioning is also feasible [32]. Patients with low platelet counts (<50 × 10^9/L) could be enrolled in a clinical trial to receive pacritinib, another JAK inhibitor that was well-tolerated and induced spleen and symptom response in patients with MF in early-phase studies [34], during 3–4 months before transplantation. Our recommendation is to make ruxolitinib available in the pre-transplant setting for patients with splenomegaly or heavy symptom burden, but more results are needed to confirm its positive impact on post-transplant outcomes.

Dose optimization and monitoring parameters of patients under ruxolitinib

A complete blood cell count must be performed before initiating ruxolitinib, and starting doses should be adapted on a case-by-case basis [35]. Various clinical parameters (e.g. renal or hepatic impairment) and potential drug interactions (e.g. potent CYP3A4 inhibitors) must be assessed [15,35]. Due to the immunosuppressive effect of ruxolitinib, the absence of active infection should be confirmed, careful evaluations of hepatitis B and latent tuberculosis infections are required, and vaccination of patients against pneumococcal diseases is recommended [15,36].

Belgian reimbursement criteria limit ruxolitinib use to MF patients with <10% blasts in peripheral blood and platelet count ≥50 × 10^9/L (>100 × 10^9/L in the previous recommendations) [15,28]. Maximum starting doses of ruxolitinib should be 5, 10, 15, and 20 mg twice daily for MF patients with baseline platelet count between 50–<75, 75–<100, 100–<200, and ≥200 × 10^9/L, respectively [35]. Based on efficacy and safety, doses may be gradually increased by a maximum of 5 mg twice daily, up to the maximum dose of 25 mg twice daily [35].

MF patients should be closely monitored during initial treatment phases, and doses should be optimized depending on spleen volume and symptom evolutions [15]. Based on our experience, the best practice includes a visit every 2 weeks during the first month to ensure that ruxolitinib is well-tolerated and evaluate blood cell counts. Of note, starting doses should not be increased within the first 4 weeks of treatment [35]. Thereafter, intervals between increases in doses should be ≥2 weeks [35]. Ruxolitinib dose optimization in case of insufficient response or after dose reductions due to adverse events (AEs) and monitoring of patients on stable doses should be performed as described in the previous recommendations [15].

Management of ruxolitinib-related adverse events

Anemia

Anemia is one of the minor MF diagnostic criteria [37] and an adverse prognostic factor (35%–54% of patients with primary MF have anemia at diagnosis [38]), and was reported in 83.8% of patients treated with ruxolitinib in clinical studies [35]. A drop in Hb levels may occur in the first weeks of treatment to reach nadir after 8–12 weeks before gradually returning to near baseline values [38]. Ruxolitinib-related anemia, as opposed to disease-related anemia, was not associated with shortened survival in MF patients [38].

In the Phase II REALISE study, an alternative ruxolitinib dosing regimen (10 mg twice daily for 12 weeks, then up-titrations if appropriate) was evaluated in anemic MF patients (Hb levels <10 g/dL). After 24 weeks, 28/50 patients, and 6/9 transfusion-dependent patients at baseline, had ≥50% spleen length reductions. Hb levels dropped in the first weeks in 82.4% of patients, but median Hb levels remained reasonably constant with support of red blood cell (RBC) transfusions as needed [39]. The mean number of transfused RBC units per 4 weeks decreased from 3.8 at baseline to 0.5–1.8 after 48 weeks in transfusion dependent patients and remained stable in non-transfusion dependent patients (around 0.5–1.0 units). In the light of these data, we recommend a ruxolitinib starting dose of 10 mg twice daily for 12 weeks in anemic patients, with a close clinical and biological follow-up to assess transfusion need. The use of RBC transfusions to treat temporary decreases in Hb levels should be a case-by-case decision.

Besides RBC transfusions and dose adjustments, erythropoiesis-stimulating agents (ESAs) can be used to manage anemia [40,41]. In principle, ESAs may activate the JAK pathway and could potentially be less effective in the presence of JAK inhibitors by counteracting ruxolitinib-induced reduction in spleen size [41]. Nevertheless, a *post-hoc* analysis of COMFORT-II suggested that ESA administration in 13 MF patients was well-tolerated and had no impact on ruxolitinib efficacy [40]. Improvements in hemoglobin abnormalities were observed in 7/13 patients within 6 weeks. A retrospective study in 59 anemic ruxolitinib-treated

MF patients confirmed that ESAs are well-tolerated and effective [41]. Anemia response rate was 54%, and 95% and 76% of patients were still responding after 4 and 5 years. In this study, anemia response rates were higher in ruxolitinib responders versus non-responsive patients. Moreover, endogenous erythropoietin (EPO) levels <125 mU/mL correlated with higher anemia response rates versus higher EPO levels (63% versus 20%; p=0.008). In the light of these new data, we propose the use of ESAs in ruxolitinib-treated MF patients, taking into account that the highest efficacy is seen in patients with EPO levels <125 mU/mL and that starting ESA does not make sense when EPO levels are >500 mU/mL [29]. Previous studies have suggested that ESAs have a limited activity in transfusion-dependent patients with primary MF and increase the risk of leukemia transformation and splenomegaly [42]. In these patients, the risk-benefit balance should thus be evaluated. We recommend stopping ESAs after 4 months if no benefit (no anemia response) is observed or if Hb levels increase to >11 g/dL.

A potential future treatment for anemia in MF patients is luspatercept, a recombinant fusion protein acting as transforming growth factor (TGF)-β superfamily ligand [43]. TGF-β ligands, through their binding to activin receptors, are involved in modulating the differentiation of late-stage erythrocyte precursors in the bone marrow. Luspatercept diminishes SMAD2 and SMAD3 signaling and enhances late-stage erythropoiesis. In a phase II study in anemic patients with MF, luspatercept was investigated as a monotherapy and in combination with JAK inhibition, showing promising results in the reduction of RBC transfusion burden [44]. Based on these results, a double-blind, phase III, randomized study is ongoing to compare luspatercept versus placebo in transfusion-dependent patients with MF on concomitant JAK inhibitor therapy.

Thrombocytopenia

Thrombocytopenia (platelet count <100 × 10^9/L) is observed in approximately 25% of patients with MF [45]. In clinical studies, approximately 80% of ruxolitinib-treated patients reported thrombocytopenia [35]. Decreases in platelet levels are expected in the first 4–12 weeks of treatment, but levels remain stable afterwards [22,46]. An analysis on 2233 patients (138 patients with platelet levels <100 × 10^9/L) from the JUMP study showed that grade 3–4 thrombocytopenia led to treatment discontinuation in only 3.4% of cases (10.1% of patients with low platelet levels) [21]. Among patients with low platelet levels, 54.5% and 29.5% of those who started ruxolitinib treatment at a dose of 5 mg twice daily, and 76.9% and 46.2% of those starting at higher doses had dose reductions and dose interruptions, respectively [21]. In the light of these results, we believe that the recommendation to reduce the dose for patients with platelet count declines to <125 × 10^9/L depending on the dose at the time of the platelet count decrease is appropriate [35]. The treatment should be stopped in patients with platelet count <50 × 10^9/L [35].

Non-hematologic adverse events

Ruxolitinib is infrequently discontinued due to non-hematologic AEs. The most common non-hematologic AEs of ruxolitinib in MF patients include fatigue, diarrhea, ecchymosis, dyspnea, dizziness, pain in extremity, headache, and nausea [16,17]. Other important side effects are weight gain and increased cholesterol and triglyceride levels, which should be monitored to control the cardiovascular risk factors in these patients [35].

Since ruxolitinib could be associated with reactivation or acquisition of infections, such as urinary tract infections, herpes zoster, tuberculosis, and hepatitis B [47], increased vigilance for opportunistic infections is recommended in ruxolitinib-treated MF patients, as suggested in our previous recommendations [15]. While systematic prophylaxis against herpes zoster is not necessary, patients should receive prophylactic aciclovir (400 mg twice daily) after an acute episode [47]. While two herpes zoster vaccines (*Zostavax*, Merck & Co., Inc [48] and *Shingrix*, GSK [49]) are licensed in Europe, they are currently not reimbursed in Belgium and systematic vaccination against herpes zoster is not recommended for any target population [50]. In patients with a positive hepatitis B serology, antiviral therapy (tenofovir/entecavir or lamivudine following discussion with a hepatologist) should be started together with monthly hepatitis B DNA monitoring [15,51]. In patients with latent tuberculosis, isoniazid (300 mg daily) should be prescribed [47].

Recent data suggested that the risk of second primary malignancy (SPM) may be increased in MF patients treated with ruxolitinib due to its immunosuppressive activity [18,52,53]. While no difference in non-melanoma skin cancer (NMSC) occurrence was detected between ruxolitinib- and placebo-treated patients in the COMFORT-I study [19], a tendency towards increased risk for NMSC was observed post-ruxolitinib treatment in the COMFORT-II study [18], a real-world safety study [54], and a retrospective study [55]. Therefore, we recommend periodic skin screening for ruxolitinib-treated patients, especially after a prolonged hydroxycarbamide therapy [56]. In patients with MF and a history of NMSC, our recommendation is to initiate and continue ruxolitinib treatment, except in those with a recurrent or aggressive NMSC who should discuss their treatment options with their oncologists [57]. For other SPM, no increased risk was demonstrated in ruxolitinib-treated patients

in the COMFORT-I study and a real-world safety study [19,54]. However, male sex, previous arterial thrombosis, and platelet count >400 × 10^9/L at ruxolitinib initiation were retrospectively identified as risk factors for SPM excluding NMSCs [56]. Therefore, we recommend that previous or new onset thromboses trigger screening for underlying SPM in ruxolitinib-exposed MF patients. Finally, aggressive B-cell non-Hodgkin lymphomas arising from pre-existing malignant B-cell clones under ruxolitinib have recently raised concern [52,54]. However, no increased risk for B-cell non-Hodgkin lymphomas was detected in ruxolitinib-treated patients in the COMFORT-I study and in a large retrospective study [19,58], and more data are needed to make recommendations here. Before starting ruxolitinib, clinical awareness regarding the presence of lymphoma is of course warranted.

Interruption, failure, stopping rules, and rechallenge

In the COMFORT studies, treatment was discontinued within 5 years in approximately 73% of MF patients [18,19]. While there is no clear worldwide consensus concerning ruxolitinib failure criteria, potential causes include resistance (primary resistance, which is very uncommon [2% to 5%], suboptimal response, or relapse/loss of response), intolerance (side effects or hematological intolerance), disease progression, second cancers or infectious complications [57,59,60]. Potential predictors of ruxolitinib resistance have been studied. Patients with pronounced splenomegaly (≥10 cm below the costal margin), a ≥2-year time interval between MF diagnosis and initiation of ruxolitinib treatment, or transfusion dependency were less likely to have a spleen response with ruxolitinib [24]. Genetic criteria such as *RAS/CBL* and HMR mutations may also predict a shorter time to JAK inhibitor-failure [61,62]. According to Belgian reimbursement criteria, periodical treatment efficacy evaluations are performed (at least every 6 months) for treatment prolongations. In intermediate-1-risk MF patients, ruxolitinib is continued if an effect is observed in terms of both spleen size and disease-related symptoms. In intermediate-2- and high-risk MF patients, decreases in spleen size or symptom improvements are sufficient to continue treatment [28]. Our recommendation remains to continue ruxolitinib treatment as long as there is clinical benefit in terms of spleen response (based on spleen volume rather than spleen length or physical examination if possible [63]) and symptoms responses (evaluated with a scoring system such as MPN10 [64]).

Sudden ruxolitinib discontinuation may induce ruxolitinib discontinuation syndrome (RDS), characterized by symptoms reactivation within 1–3 weeks, rapid disease progression, worsening cytopenia, and rapidly increasing splenomegaly, potentially leading to hemodynamic instability, shock, acute respiratory distress syndrome, and cytokine release syndrome [35,65]. In a recent survey, RDS was reported in 34/251 patients and severe RDS in 3/251 patients who stopped ruxolitinib treatment abruptly or according to various tapering strategies [65]. Platelet count <100 × 10^9/L and spleen lengths ≥10 cm from LCM were identified as risk factors for RDS. Although discontinuation strategies are not standardized, our recommendation remains to stop the treatment by reducing the dose by 5 mg twice daily every week with careful monitoring [15]. In patients at increased risk, prophylactic corticosteroids should be introduced. When a RDS occurs, ruxolitinib can be restarted or treatment with another JAK inhibitor can be initiated (currently not possible in Belgium since only ruxolitinib is reimbursed for MF patients).

After ruxolitinib discontinuation, patients may respond to a ruxolitinib rechallenge (re-exposure to ruxolitinib for ≥2 weeks, with ≥2 weeks between courses) [66]. In an observational study evaluating rechallenge in 60 patients who discontinued ruxolitinib (≥2 weeks) due to intolerance (70%) or inadequate response (30%), 44.6% and 48.3% of patients had spleen and symptom improvements [66]. At 1 and 2 years, 33.3% and 48.3% of rechallenged patients had permanently discontinued ruxolitinib. The median OS was significantly longer for the 60 rechallenged patients versus 159 patients who permanently stopped ruxolitinib (41.1 versus 23.7 months; p=0.004). Since new agents are under investigation, including second-line JAK inhibitors, we recommend including eligible patient in clinical trials after ruxolitinib discontinuation. In other cases, ruxolitinib rechallenge can be considered a safe and potentially beneficial option for patients who discontinued ruxolitinib for ≥2 week due to intolerance and have exhausted other standard therapies.

Conclusion

Ruxolitinib is the JAK inhibitor with the longest safety and efficacy follow-up for the treatment of MF patients. In Belgium, ruxolitinib is approved and reimbursed for HSCT-ineligible IPSS intermediate-2- and high-risk MF patients and IPSS intermediate-1-risk MF patients with splenomegaly. While low- and intermediate-1-risk MF patients without splenomegaly could also benefit from symptom improvements, more results are needed to make recommendations for the use of ruxolitinib alone or in combination with other drugs in this population. Further studies should also evaluate the impact of the mutational status and symptom burden on ruxolitinib efficacy in this population. In the pre-HSCT setting, we believe that ruxolitinib should be made available for MF patients with

splenomegaly or heavy symptom burden since it may lead to improved post-HSCT outcomes.

In ruxolitinib-treated MF patients, blood cell counts should be closely monitored, and ruxolitinib doses should be adapted on a case-by-case basis. In anemic patients, starting doses of ruxolitinib should be 10 mg twice daily for the first 12 weeks, with blood tests performed every week. ESAs may be tried in patients with EPO levels ≤500 mU/mL. The optimal efficacy of ESAs is, however, seen when EPO levels are <125 mU/mL. Increased vigilance for opportunistic infections and SPMs is needed in ruxolitinib-treated MF patients. Our recommendation remains to continue ruxolitinib treatment as long as there is clinical benefit, and to use progressive dose tapering for ruxolitinib discontinuation to reduce the risk of RDS.

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