Review of Treatment Options for Myelofibrosis: Focus on Ruxolitinib

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Abstract: In November 2011, the United States Food and Drug Administration (FDA) approved the use of a novel Janus Kinase (JAK) 1/JAK2 inhibitor, INCB 018424 (ruxolitinib), for use in both intermediate and high risk myelofibrosis. Approvals of this agent in both Canada and Europe have followed most recently. The European Medicines Agency (EMA) concluded that ruxolitinib was indicated for disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera (PV) myelofibrosis, and post-essential thrombocythaemia (ET) myelofibrosis. In this review we will consider the rationale for targeting of the JAK-pathway, discuss the pharmacological profile of ruxolitinib and review the currently available clinical trial data. We will also postulate on the current and potential future roles of ruxolitinib within the MPN field.

Keywords: myeloproliferative, myelofibrosis, Janus Kinase, ruxolitinib

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**Introduction**

Primary myelofibrosis (PMF) is a chronic myeloproliferative neoplasm (MPN) associated with clonal proliferation of aberrant haematopoietic progenitors. Augmented pro-inflammatory and pro-angiogenic cytokine deregulation ensues, with associated bone marrow fibrosis. It is a rare and heterogeneous disorder, with a postulated incidence of almost 1.5/100 000 of the population.

The heterogeneity of myelofibrosis (MF) extends not only to the clinical phenotype, but also to the many molecular aberrations that may be associated with disease pathogenesis, and it presents many challenges for the treating clinician. The spectrum of symptoms may include marked constitutional symptoms, pruritus, symptomatic splenomegaly, bone discomfort and infective complications. Furthermore, variable degrees of cytopenias, or indeed leukocytosis/thrombocytosis in some cases, may occur in addition to thrombotic or haemorrhagic phenomena. The clinical course may range from an aggressive disease in some individuals, with a survival measured in months, to a more indolent disease in others. There is an inherent risk of leukaemic transformation and the outcome of MF in blast phase (MF-BP) is often dismal.

MF can arise in patients with a prior diagnosis of polycythaemia vera (PV) or essential thrombocythaemia (ET), so called secondary MF (sMF).

In regards to risk stratification at diagnosis, the International Prognostic Scoring system (IPSS) has become the most widely adapted system used in clinical practice. Based on five clinicopathological variables (anaemia (Haemoglobin < 10 g/dL), age > 65 years, leukocytosis > 25 × 10^9/L, peripheral blasts ≥1% and the presence of constitutional symptoms) patients can be subdivided into four distinct prognostic groups. These are low risk (0 risk factors, median survival 135 months), intermediate-1 (1 risk factor, median survival 95 months), intermediate-2 (2 risk factors, median survival 48 months) and high risk (3 or more risk factors, median survival 27 months). It should be noted that the IPSS is derived from patients with PMF but in clinical practice is often used for those with sMF as well. Subsequent refinements of the IPSS to the Dynamic IPSS (DIPSS), which can be applied as an indication of prognosis at any stage in the disease course, and with further risk factors within the ‘DIPSS plus’, including thrombocytopenia (Platelets < 100 × 10^9/L), karyotype abnormalities (including complex karyotypes and +8, −7/7q−, i (17q), inv(3), −5/5q−, 12p−, 11q23 rearrangements), and red cell transfusion dependency, have been proposed. These scoring systems should be utilized to guide patient management and are summarized in Table 1. However there are major limitations with these analyses: first that they have not been validated in patients with sMF and second that the DIPSS plus is often incorrectly quoted and utilized with a misunderstanding that the score reflects the total number of prognostic factors, which is not the case. Additionally, the DIPSS plus does not appear to further enhance our ability to stratify patients in the lower risk groups as intermediate I and high risk are closer together here in their median life expectancy (1.3–6.5 years) than using the DIPSS where the range is 1.5–14.5 years. It is clear that these prognostic systems require refinement.

Historically, the symptom-directed treatments available for MF have often been limited in both efficacy and specificity. Therapeutic options have included best supportive care/transfusion support, cytoreduction with either hydroxyurea or interferon, the use of erythropoietin stimulating agents, immunomodulatory drugs such as thalidomide and lenalidomide, danazol, radiotherapy and splenectomy. The British Committee for Standards in Haematology have recently produced guidelines for the diagnosis and management of myelofibrosis which review these therapeutic options in detail and add to the international recommendations in this field. Trials of pomalidomide have been somewhat encouraging, as regards an improvement in anaemia, and a phase III study with this agent is expected to be published in 2013. Additionally, both Akt/mTOR as well as Histone Deacetylase Inhibition are areas of active investigation. There are also numerous early phase studies investigating other therapeutic targets. However, the only definitive curative option for MF is Allogeneic Stem Cell Transplantation, which is not a viable therapeutic option for a large proportion of patients (reviewed by McLornan et al.). Furthermore, until recently, no treatments for MF had been evaluated in phase III studies nor had any been shown to ameliorate the burden of constitutional symptoms or improve quality of life for MF patients.

In November 2011, the United States Food and Drug Administration (FDA) approved the use of a novel Janus Kinase (JAK) 1/JAK2 inhibitor, INCB
Ruxolitinib in myelofibrosis

Table 1. Current prognostic scoring systems for MF.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>IPSS</th>
<th>DIPSS</th>
<th>DIPSS-plus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of adverse prognostic factors</td>
<td>Median survival, years</td>
<td>No. of adverse prognostic factors</td>
</tr>
<tr>
<td>Low risk</td>
<td>0</td>
<td>11.3</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>1</td>
<td>7.9</td>
<td>1–2</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>2</td>
<td>4.0</td>
<td>3–4</td>
</tr>
<tr>
<td>High risk</td>
<td>≥3</td>
<td>2.3</td>
<td>5–6</td>
</tr>
</tbody>
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Note: *This is the risk group NOT the sum of points.

018424 (ruxolitinib), for use in both intermediate and high risk PMF and sMF. Approvals of this agent in both Canada and Europe have followed most recently. In this review, we will summarize the rationale for targeting of the JAK-pathway, discuss the pharmacological profile of ruxolitinib and review the currently available clinical trial data. We will also postulate on the current and potential future roles of ruxolitinib within the MPN field.

Targeting the JAK-pathway: rationale for the use of ruxolitinib

The JAK family consists of JAK1, JAK2, JAK3 and Tyrosine Kinase-2 (TyK2), all of which are non-receptor protein tyrosine kinases. In 2005, four independent research groups published seminal papers on the discovery of a gain-of-function mutation in the JAK2 gene in Philadelphia-chromosome negative MPN disorders.\(^\text{14–17}\) The prevalence of the JAK2 V617F mutation varies within the MPN subtypes, being present in almost all patients with PV, and in up to 60% in both MF and ET. Constitutive activation of JAK2 results from a valine-to-pheno\(\ldots\)lalanine substitution at amino acid position 617 within the JAK Homology 2 (JH2) pseudokinase domain, with a resultant loss of kinase auto-inhibition. Downstream ligand-independent activation of signal transducer and activator of transcription (STAT) 3/5, RAS-mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathways occurs with modulation of cell differentiation, enhanced proliferation, and promotion of a pro-survival phenotype. In addition, recent work has demonstrated a nuclear role for constitutively active JAK2 in phosphorylation of Histone-3 Tyrosine 41 (H3Y41), leading to decreased binding of Heterochromatin Protein-1 α (HP1α) to heterochromatin.\(^\text{18}\) Resultant transcriptional dysregulation induces changes in several key genes, including up-regulation of the ‘leukaemogenic’ Lim Domain Only-2 (LOM2) gene. JAK2 inhibitors have been shown to inhibit H3Y41 phosphorylation both in vitro and in vivo.\(^\text{18}\) Moreover, JAK-STAT pathway dysregulation is characteristic of patients with MF, either in the presence or absence of the JAK2 V617F mutation, and hence makes this pathway an attractive therapeutic target.\(^\text{19}\)

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Ruxolitinib ((R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate) acts as a potent and selective inhibitor of both JAK1 (half maximal inhibitory concentration IC\(_{50}\) = 3.3 nanomolar (nM)) and JAK2
When murine Ba/F3-EpoR-JAK2V617F cells, displaying constitutive phosphorylation of JAK2 were treated with ruxolitinib, proportional inhibition of JAK2V617F, STAT5 and ERK1/2 phosphorylation occurred with a reduction in both cellular apoptotic threshold and proliferative capacity. In a murine MPN model, subsequent in vivo work revealed that ruxolitinib therapy induced reductions in both splenomegaly and neoplastic cell burden and led to a relative improvement in survival. This was accompanied by significant reductions in both Interleukin-6 (IL-6) and Tumor Necrosis Factor (TNF) α. Furthermore, ruxolitinib was shown to preferentially inhibit growth of ex vivo expanded erythroid colonies derived from patients with JAK2 V61F PV when compared to healthy controls.

The results obtained from this preclinical characterization of ruxolitinib led to rapid introduction into early phase clinical trials. Ruxolitinib is available for clinical use in tablet formulation. In healthy volunteers, single oral dose administration of ruxolitinib (dose range, 5–200 milligrams (mg)) demonstrated rapid absorption, with achievement of peak plasma concentrations within two hours. Both the maximum plasma drug concentration (Cmax) and the Area Under the plasma Concentration time curve (AUC) displayed linear pharmacokinetics (PK) and were independent of saturable transporter systems. The drug is highly protein bound in plasma, as reflected by its relatively small volume of distribution, and has an approximate 3-hour terminal-phase elimination half-life in plasma. Although body weight was found to be a significant covariate in the central volume of distribution (Vc/F) in MF patients, no dose adjustments are required. Combined PK modeling from the early ruxolitinib trials (INCB 18424-251, INCB 18424-351 and INCB 18424-352), suggests that female patients have a slightly lower apparent clearance of ruxolitinib compared to male patients (17.7 L/h compared to 22.1 L/h). Trial data also supports that ruxolitinib does not display significant accumulation or changes within the PK profile on chronic dosing with the therapeutic regimens of 5–25 mg twice daily (BD).

On pharmacodynamic profiling, dose- and time-dependent reversible inhibition of cytokine-induced phosphorylated STAT3 was detected in the analyzed cell extracts from the healthy volunteer study. Negligible accumulation of ruxolitinib or metabolites were discovered on analysis of the PK/pharmacodynamic (PD) models for both exploratory single and BD dosing and, reassuringly, none of the study individuals demonstrated significant evidence of PK/PD hysteresis. The effect of food intake on a single dose of 25 mgs was further evaluated in healthy individuals who were fasting or immediately post a high caloric/high fat content meal. Negligible difference in drug AUC between each group was identified, clinically indicating little effect of food on the timing of ruxolitinib administration.

Ruxolitinib is extensively metabolized in humans, mainly by the most prevalent hepatic cytochrome P450 enzyme CYP3A4, with less than 1% of parent drug being excreted. Predominant metabolites are hydroxyl- or oxy-derivatives, a proportion of which are subject to O-glucuronidation. The main route of end-product excretion is in the urine. The effects of both CYP3A4 inhibition and induction on the PK/PD profile of single dose ruxolitinib has also been recently reported. Co-administration of the potent CYP3A4 inhibitor, ketoconazole, led to a 91% increase in total ruxolitinib plasma exposure following a single dose and had a correlative effect on PD. Co-treatment with rifampicin, a known CYP3A4 inducer, led to a reduction in total plasma exposure by 71% but, in contrast, had less effect on the PD profile. This is potentially due to a relatively minimal effect on ruxolitinib’s active metabolites.

Potential clinically relevant interactions with ruxolitinib would therefore include CYP3A4 inhibitors such as the azole family, macrolide antibiotics such as clarithromycin, calcium channel blockers such as verapamil and protease inhibitors such as ritonavir and saquinavir. PK/PD data suggests a 50% dose reduction in those treated with drugs such as ketoconazole; however, this is yet to be validated in human trials.

Clinical Studies and Efficacy

A Phase I/II trial of ruxolitinib in MF (INCB018424-251; ClinicalTrials.gov, NCT00509899), coordinated between the Mayo Clinic, Rochester and MD Anderson Cancer Centre, Houston, enrolled 153 patients (PMF n = 81; sMF n = 72) with a median follow-up of 14.7 months. The median age was (IC50 = 2.8 nM)) when studied within in vitro model systems. When murine Ba/F3-EpoR-JAK2V617F cells, displaying constitutive phosphorylation of JAK2 were treated with ruxolitinib, proportional inhibition of JAK2V617F, STAT5 and ERK1/2 phosphorylation occurred with a reduction in both cellular apoptotic threshold and proliferative capacity. In a murine MPN model, subsequent in vivo work revealed that ruxolitinib therapy induced reductions in both splenomegaly and neoplastic cell burden and led to a relative improvement in survival. This was accompanied by significant reductions in both Interleukin-6 (IL-6) and Tumor Necrosis Factor (TNF) α. Furthermore, ruxolitinib was shown to preferentially inhibit growth of ex vivo expanded erythroid colonies derived from patients with JAK2 V61F PV when compared to healthy controls. The results obtained from this preclinical characterization of ruxolitinib led to rapid introduction into early phase clinical trials. Ruxolitinib is available for clinical use in tablet formulation. In healthy volunteers, single oral dose administration of ruxolitinib (dose range, 5–200 milligrams (mg)) demonstrated rapid absorption, with achievement of peak plasma concentrations within two hours. Both the maximum plasma drug concentration (Cmax) and the Area Under the plasma Concentration time curve (AUC) displayed linear pharmacokinetics (PK) and were independent of saturable transporter systems. The drug is highly protein bound in plasma, as reflected by its relatively small volume of distribution, and has an approximate 3-hour terminal-phase elimination half-life in plasma. Although body weight was found to be a significant covariate in the central volume of distribution (Vc/F) in MF patients, no dose adjustments are required. Combined PK modeling from the early ruxolitinib trials (INCB 18424-251, INCB 18424-351 and INCB 18424-352), suggests that female patients have a slightly lower apparent clearance of ruxolitinib compared to male patients (17.7 L/h compared to 22.1 L/h). Trial data also supports that ruxolitinib does not display significant accumulation or changes within the PK profile on chronic dosing with the therapeutic regimens of 5–25 mg twice daily (BD).

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65 years (range, 40–84), approximately 2/3 were classified as IPSS high risk disease, and the median number of prior MF-directed therapies was 2 (range, 0–15). Dose escalation studies initially determined an efficacious and safe starting dose of 15 mgs twice daily as the main dose-limiting toxicity factor was thrombocytopenia. Significant, rapid and durable reductions in spleen size occurred in responding patients, often commencing within the first or second month of therapy, and occurred irrespective of JAK2 V617F mutation status or MF disease type (PMF versus sMF). A majority of individuals with debilitating MF-related symptoms had >50% amelioration in symptom scores according to the Myelofibrosis Symptom Assessment Form (MF-SAF). The main haematological toxicity comprised anaemia and thrombocytopenia. Non-haematological adverse events were uncommon, occurring in less than 10% of patients, and included diarrhea, fatigue, headache, peripheral oedema, pain in the extremities and dizziness. Grade III and IV adverse events were unusual and incorporated fatigue (1.3%), asthenia (2.0%), anxiety (1.3%), insomnia (1.3%), and fever (0.7%). In those patients with the JAK2 V617F mutation, modest reductions in the JAK2 V617F allele burden were noted (mean maximal suppression in allele burden from baseline approximated 13% following 48 weeks of therapy (n = 34). In keeping with the \textit{in vitro} data discussed above, cytokine profiling revealed ruxolitinib-induced reductions in plasma levels of key pro-inflammatory cytokines including IL-1, TNFα, macrophage inflammatory protein (MIP)-1β and IL-6 which actually correlated with improvement in symptoms. Furthermore, it is plausible that extramedullary haematopoesis-associated splenomegaly may well be particularly dependent upon dysregulated JAK-STAT signaling or resultant cytokine disarray and hence explain the observed clinical responses as regards spleen size reduction.\textsuperscript{25}

Two pivotal Phase III studies, entitled Controlled MyeloFibrosis Study with Oral JAK Inhibitor Therapy (COMFORT)-I and COMFORT-II respectively, were published in March 2012.\textsuperscript{26,27} COMFORT-I was a placebo-controlled trial, enrolling a total of 309 patients with IPSS intermediate-2 (38.2%) or high Risk (61.2%) MF and randomizing in a 1:1 fashion to either twice daily ruxolitinib, with permitted dose adjustment, or placebo.\textsuperscript{26} Patients on treatment received either 15 mg BD (platelet count 100–200 × 10\(^9\)/L) or 20 mg BD (platelet count > 200 × 10\(^9\)/L).\textsuperscript{26} A total of 36 patients in the placebo group crossed over to the treatment arm, 16 doing so prior to week 24 and 20 thereafter and ultimately the majority of patients crossed as per study protocol. Striking results were obtained, with approximately 42% of patients in the ruxolitinib treated cohort reaching the primary end point of a ≥35% reduction in spleen size at 24 weeks, compared to 0.7% in the placebo-control arm (\(P < 0.001\)). Furthermore, on analysis of the modified MF-SAF (version 2), a significant proportion of patients in the ruxolitinib treated cohort had a reduction of at least 50% in the total MF SAF symptom score at week 24 compared to those in the control cohort (45.9% vs. 5.3%; \(P < 0.001\)). Importantly, symptom improvement occurred irrespective of IPSS risk group, age, gender, JAK2 mutation status, spleen size, or haemoglobin. In contrast, the majority of those in the placebo arm demonstrated a worsening in the mean Total Symptom Score. There were a total of 13 deaths in the ruxolitinib arm versus 24 in the placebo arm (\(P = 0.04\)), potentially alluding to a possible survival advantage. Within the companion COMFORT-II study, 219 adult patients with intermediate-II or high risk PMF/sMF were randomized over a seven-month period in a 2:1 fashion to receive either ruxolitinib (n = 146) or Best Available Therapy (BAT, n = 73).\textsuperscript{27} At week 48, the percentage of patients achieving a spleen volume reduction of ≥35% was 28.5% with ruxolitinib versus 0% with BAT (\(P < 0.001\)). Dose limiting toxicity was again thrombocytopenia, but was reversible. The most common non-haematological grade 3 or 4 adverse effects (ruxolitinib versus BAT) were diarrhea (23% versus 12%), peripheral oedema (22% versus 26%), and asthenia (18% versus 10%). Both Disease Related Symptoms (DRS) and Quality of Life (QOL) were assessed objectively by the European Organization for Research and Treatment of Cancer (EORTC) QOL questionnaire core model (QLQ-C30) in addition to the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) scale questionnaire. Assessments were performed at baseline as well as at weeks 8, 16, 24 and 48. In keeping with data from COMFORT-I, analysis revealed a significant beneficial effect of ruxolitinib compared to BAT on appetite loss, fatigue, pain, insomnia, dyspnoea, and physical and role functioning that was
apparent at week 8 and remained present in those still on the drug at week 48. Moreover, these beneficial effects were not significantly different between the high risk and intermediate-2 risk groups on further sub-analyses. Correlations between plasma cytokine levels and splenic size suggested that reductions in TNFα and increases in Leptin paralleled reductions in splenomegaly at both week 24 and week 48 of therapy. Interestingly, although beneficial effects can occur irrespective of JAK2 mutation status, in the ruxolitinib arm, significantly more patients who achieved a ≥20% decrease in JAK2 V617F allelic burden gained a ≥35% decrease in splenic size compared to those who achieved <10% decrease in JAK2 V617F allelic burden (79% versus 30%).

Earlier this year, an update of the 107 patients enrolled in the MD Anderson Phase I/II cohort revealed discontinuation rates at 1, 2, and 3 years of 24%, 36%, and 46% respectively, with a median follow up period of 32 months. On comparison to a cohort of 310-matched historical control patients, there was a significant overall survival benefit evident for those treated with ruxolitinib after adjustment for IPSS risk group (P = 0.005). Sub-analyses revealed highly significant differences in OS within the high risk disease subgroup (3-year OS rate in the ruxolitinib group = 63% versus historical control = 35%). High risk patients treated with ruxolitinib gained a similar OS to that of Intermediate-II patients treated with drug. The degree of reduction in splenic size correlated strongly with survival benefits.

In contrast to this promising data on improved survival, an update from the Mayo clinic cohort (n = 51) suggested significantly higher treatment discontinuation rates at 1, 2, and 3 years of 51%, 72%, and 89% respectively and no actual survival advantage was evident on comparison to historical controls (n = 410). Definitive conclusions, however, are limited due to the smaller cohort size. Importantly, the mean total daily dose of ruxolitinib in the MD Anderson cohort was actually higher than that in the Mayo Clinic Cohort (near 31 mg). As recently suggested, the lack of survival benefit in the smaller Mayo Clinic cohort may well be a reflection of lower dosages and the high discontinuation rate in this cohort (ie, a reduced overall drug exposure).

As discussed above, the main dose-limiting toxicity of ruxolitinib in MF is reversible thrombocytopenia. Alternate dosing strategies are currently being investigated in MF patients with platelet counts between 50–100 × 10^9/L in a phase II, open label trial of 24 weeks duration. The starting dose is 5 mgs twice daily, and dose optimization may occur on a 4-weekly basis dependent on toxicity. Interim analysis (n = 41) has shown that only 4 patients required dose interruption due to a fall in platelet count to <25 × 10^9/L. Despite attenuated dosing, the majority of patients on the drug experienced significant improvements in symptoms and reductions in spleen length. These initial findings are very encouraging and demonstrate potential benefits at lower dosages in this group of patients. A further Phase 1b trial, entitled EXPAND (Evaluating Ruxolitinib in Patients with Low Baseline Platelet Counts Diagnosed with Myelofibrosis) is currently investigating the maximum safe starting dose of ruxolitinib in those with platelets between 50–99 × 10^9/L and, importantly, will also have an extension phase-post week-24 to delineate long term efficacy and side effects.

Despite the obvious benefits from ruxolitinib therapy in the MF population, long term follow up data from of all of the available studies is required. It is important to contrast the results with ruxolitinib with the BCR/ABL inhibitors where molecular remissions are attainable. Furthermore, point mutations have been shown to generate in vitro resistance to these agents in CML. Data is beginning to emerge regarding this problem with ruxolitinib. For example using ‘high-throughput’ in vitro screens, Deshpande recently described five non-synonymous point mutations that conferred ruxolitinib resistance in vitro and also conferred secondary resistance to a range of other JAK2 inhibitors. Whether kinase inhibitor secondary resistance will be a significant clinical issue is still unknown.

**Safety**

Throughout the ruxolitinib trials, the most significant adverse events have been the haematological toxicities, namely anaemia and thrombocytopenia. These are expected ‘on-target’ consequences. These cytopenias are both dose dependent and reversible but can necessitate dose reductions or periods of drug cessation if recurrent. Grade 3/4 thrombocytopenia was observed in 29% of patients within the 25 mg BD cohort in the initial phase I/II study with patients typically recovering their counts within 1 to 3 weeks of drug cessation. During the COMFORT-I and II trials,
early reductions in platelet counts occurred in 70% of ruxolitinib treated patients but rarely reached grade 3/4 with appropriate and timely dose modifications. More importantly, excluding ecchymosis, there was no observed increase in bleeding events.\textsuperscript{26,27}

New onset anaemia (>2 g/L drop in Hb) was observed in a dose dependent manor in the phase I/II study, such that within the 15 mg BD cohort, 8% developed anaemia with greater than half of these patients requiring red cell transfusion, whilst 27% of patients in the 25 mg BD cohort became anemic with the majority going on to require transfusion support. During the phase III trials, 96% of patients showed some reduction in haemoglobin as the “worst level on study,” with the majority (70%) in the Grade 2 and 3 range. Interestingly, this change was most marked between weeks 8 and 12 of therapy then started to reverse in most patients. In both COMFORT-I and II only 5% of patients required drug interruptions due to their anaemia. Neutropenia is also reported but was extremely rare in the clinical studies with ruxolitinib. However, increased incidence of urinary tract infections and herpes zoster infections were noted and suggests an effect of the drug upon functional immunity.

Non-haematological toxicities reported with ruxolitinib are for the most part rare and tend to be limited to Grade 1 and 2. Gastrointestinal toxicity was the most commonly reported non-haematological event with 23% of patients describing diarrhea and 13% constipation, however only 1% of patients reported severe symptoms. Other symptoms that occurred more frequently in the ruxolitinib treated patients included dizziness, headache, peripheral oedema, fatigue, pyrexia, and shortness of breath. These symptoms were however also described in the control arms of both phase III trials with relatively low differences in incidence between active and control arms.

Due to ruxolitinib’s mechanism of metabolism and excretion, caution should be taken in the context of renal and hepatic impairment. Administration of a single dose of ruxolitinib to patients with varying, degrees of renal failure, including patients on dialysis resulted in pharmacokinetics similar to that of healthy subjects. However, as the degree of renal impairment increased so too did plasma concentrations of both ruxolitinib and its active metabolites. It has therefore been recommended that patients with a creatinine clearance of less than 60 mL/min and a platelet count of <150 × 10^9/L may require a dose reduction and once rather than twice daily dosing (data obtained from ruxolitinib SPC). Elevated plasma concentrations of ruxolitinib and a prolonged drug half-life have both been shown in subjects with deranged liver function (Child-Pugh A through C).\textsuperscript{37} Dose reductions are therefore advocated for any degree of hepatic impairment in patients with a platelet count of <150 × 10^9/L; indeed once daily dosing is currently recommended for these subjects.

Pregnancy and breast feeding are relatively rare events in myelofibrotic patients with a corresponding lack of data on safety. Ruxolitinib use was associated with low birth weights and late reabsorptions in the initial mice and rabbit models. There was however no evidence of teratogenicity at any dose in these animal models. Ruxolitinib use during pregnancy and breast feeding should be avoided.

Following the initial phase I/II trial, there have been 5 cases of a systemic inflammatory response syndrome following abrupt cessation of ruxolitinib. This has been described as a cytokine rebound reaction associated with a rapid return of the patient’s splenomegaly and systemic hypercatabolic symptoms driven by proinflammatory cytokines.\textsuperscript{38} There have been no further incidents of this reaction described in either COMFORT-I or COMFORT-II. Given the large study population in the combined COMFORT cohorts, it seems unlikely that very severe drug withdrawal reactions will prove to be a significant on-going issue. However the data from COMFORT-I clearly demonstrates that disease-related symptoms will recur rapidly on drug withdrawal. This should be stated to patients and be considered in withdrawing the drug as well as the effect in may have upon the patient depending upon their clinical status at the time of withdrawal. In other words, if the patient is unstable and unwell and the drug is withdrawn, then the clinical status of the patient may deteriorate.\textsuperscript{26} Therefore if patients being treated with ruxolitinib require cessation of drug, then a tapered discontinuation has been suggested to ameliorate this risk. Consideration of corticosteroid cover was also advocated in the phase III studies.

Place in Therapy
Ruxolitinib is the first JAK 1 and 2 inhibitor to be approved for the management of MF; its route to approval involved the first ever phase III trials in
this condition. The FDA approved ruxolitinib for use in patients with intermediate and high risk MF without specifying which aspects of the disease it should be used for and without specifying whether patients must have an “adequate” blood count. In contrast, within Europe, ruxolitinib gained approval for MF patients to treat either splenomegaly or symptoms, provided the patient’s starting platelet count was at least $50 \times 10^9/L$. Recommended starting doses are 5 mg twice daily if the platelet count is $50–100 \times 10^9/L$; 15 mg twice daily where it is $100–200 \times 10^9/L$ and 20 mg twice daily if it is above $200 \times 10^9/L$; the maximum dose is 25 mg twice daily. No stage of disease, minimum degree of splenomegaly nor type or severity of symptoms are specified; nor does approval state whether the drug should be used as first or second line. On a practical basis, we use ruxolitinib in those with symptomatic/bulky splenomegaly +/- troublesome constitutional symptoms. Of note, it has been suggested that patients who achieved at least a 10% reduction in spleen size can have objective responses as regards symptoms and QOL.\textsuperscript{39} It will be important to determine the effect of this drug in those with earlier stages of disease. In the UK, the agent is undergoing a NICE (national institute of clinical excellence) appraisal, the results of which are anticipated in 2013. Results of phase III studies ruxolitinib in patients with PV and further studies with alternative JAK inhibitors are anticipated during 2013 or later.

Ruxolitinib brings a new modality of therapy to patients with MF. As we have discussed already it is well tolerated with a long median duration of response (not yet reached in current COMFORT studies), however haematological toxicity, though readily managed by dose-reduction, is a limiting factor in a subset of patients. This highlights the potential utility of combining other therapies to reduce or ameliorate haematological toxicity; examples of such combination therapies might include pomalidomide, danazol, or erythropoetin for anaemia. A further rationale for combining therapies is to deepen or improve the therapeutic efficacy of ruxolitinib. Examples of this may include stem cell transplantation, additional experimental agents such as Histone Deacetylase or mTOR Inhibitors, and interferon (α) amongst others. Several of these studies are now underway and are hoped to facilitate further major advances in the therapy of MF and, possibly, ultimately a cure. As alluded to above, a tantalizing question is whether ruxolitinib should be used earlier in the disease, when perhaps there is less genetic complexity and theoretically a greater likelihood of disease eradication or stabilization. Such a study is important but would involve large numbers of patients and long follow up. Whether use of the drug at this stage of the disease would prevent spleen progression is an important question. Of note, all patients undergoing therapy with ruxolitinib should be monitored closely to assess response (eg, objective assessment of symptoms and to ascertain if reductions in spleen size are apparent) and to detect any signs of disease progression (eg, increases in peripheral circulating blast counts). It is also important to objectively consider the role of allotransplantation for those transplant-eligible patients who have a suitable donor and are estimated to have a median survival of less than five years.

Studies (RESPONSE, RELIEF and MAJIC) are already underway in patients with either PV or ET who are resistant or refractory to standard therapy with hydroxycarbamide. These patients have a worse prognosis and appear to be at higher risk of transforming to sMF and may thus represent a useful model for earlier disease treatment or indeed in reducing the risk of transformation to sMF.\textsuperscript{40}

Conclusions

MF is a rare malignancy and the past decade has witnessed significant advances in our understanding of the clinical features of this condition and in its pathogenesis. These advances have led to the development of new therapeutic opportunities and approaches for these patients. Ruxolitinib is the first of these agents to gain approval and represents a significant therapeutic advance in this and related fields. Ruxolitinib also shows some evidence of benefit in the management of other MPNs,\textsuperscript{41} eosinophilia with JAK rearrangements,\textsuperscript{42} and possibly also AML.\textsuperscript{43} It is under investigation in patients with rheumatoid arthritis, psoriasis, non-Hodgkin’s lymphoma, breast cancer, and other conditions. Yet as witnessed with other advances in modern medicine, the development of JAK inhibition opens further opportunities and brings additional challenges. Measuring the benefit of ruxolitinib for MF patients in terms of survival advantage is of major interest and it is to be hoped that further data will be forthcoming from the two phase III studies. On-going safety monitoring is essential and indeed mandated for a drug which spec
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through the process of phase I to approval in a little over 4 years. Alternative JAK inhibitors are at various stages of development and may perhaps offer further advantages to patients (reviewed in Harrison et al). Meanwhile researchers are moving on evaluating not only other JAK inhibitors or JAK inhibitors in combination with other modalities, as we have discussed, but also additional targets in this challenging disease. The hurdle for the patient and their physician at present may include accessing ruxolitinib as approvals occur and reimbursement strategies are being put in place for such is the demand and excitement around this drug. Ruxolitinib has dramatically improved the therapeutic options for MF, where previously there were few, and offers for the first time a treatment which reduces the burden of disease. Moreover, it appears to prolong survival; an option not previously available for the majority of patients suffering from MF.

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