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MONOGRAPH

RUXOLITINIB

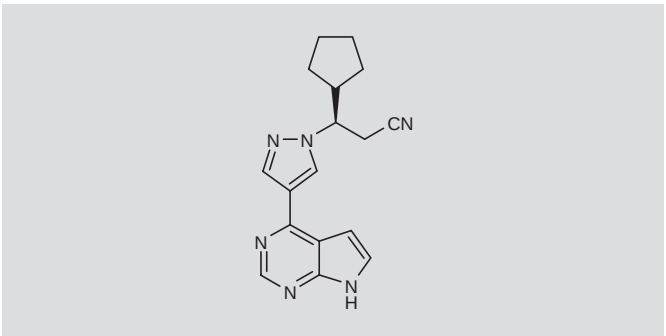
USAN

Tyrosine-Protein Kinase JAK1/2 Inhibitor
Treatment of Myelofibrosis
Treatment of Myeloproliferative Neoplasms
Treatment of Psoriasis

INC-424
INCB-18424
INCB-018424

3(*R*)-3-Cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]propanenitrile

InChI: 1S/C17H18N6/c18-7-5-15(12-3-1-2-4-12)23-10-13(9-22-23)16-14-6-8-19-17(14)21-11-20-16/h6,8-12,15H,1-5H2,(H,19,20,21)/t15-/m1/s1



$C_{17}H_{18}N_6$
Mol wt: 306.369
CAS: 941678-49-5
EN: 457842

SUMMARY

Ruxolitinib (INCB-018424) is a selective tyrosine-protein kinase JAK1 and JAK2 inhibitor that acts by blocking the JAK/STAT pathway, which plays a key role in the signaling of many cytokines and growth factors involved in cellular proliferation, growth and hematopoiesis. Ruxolitinib is being developed as an oral formulation for the treatment of several diseases, showing a good safety profile without off-target toxicities. The compound showed promising results in early clinical studies in myeloproliferative neoplasms and is currently in phase III clinical development for the treatment of myelofibrosis, either primary or secondary to polycythemia or essential thrombocythemia. Ruxolitinib is also being evaluated in phase II clinical trials for the treatment of polycythemia vera, essential thrombocythemia and secondary, post-myeloproliferative disorder acute myeloid leukemia. Its potential efficacy is being tested in other leukemias, as well as in prostate cancer and multiple myeloma. This novel JAK1/2 inhibitor is also being used topically for the treatment of psoriasis in phase II studies, and it was studied for the treatment of rheumatoid arthritis but development in this indication has been discontinued.

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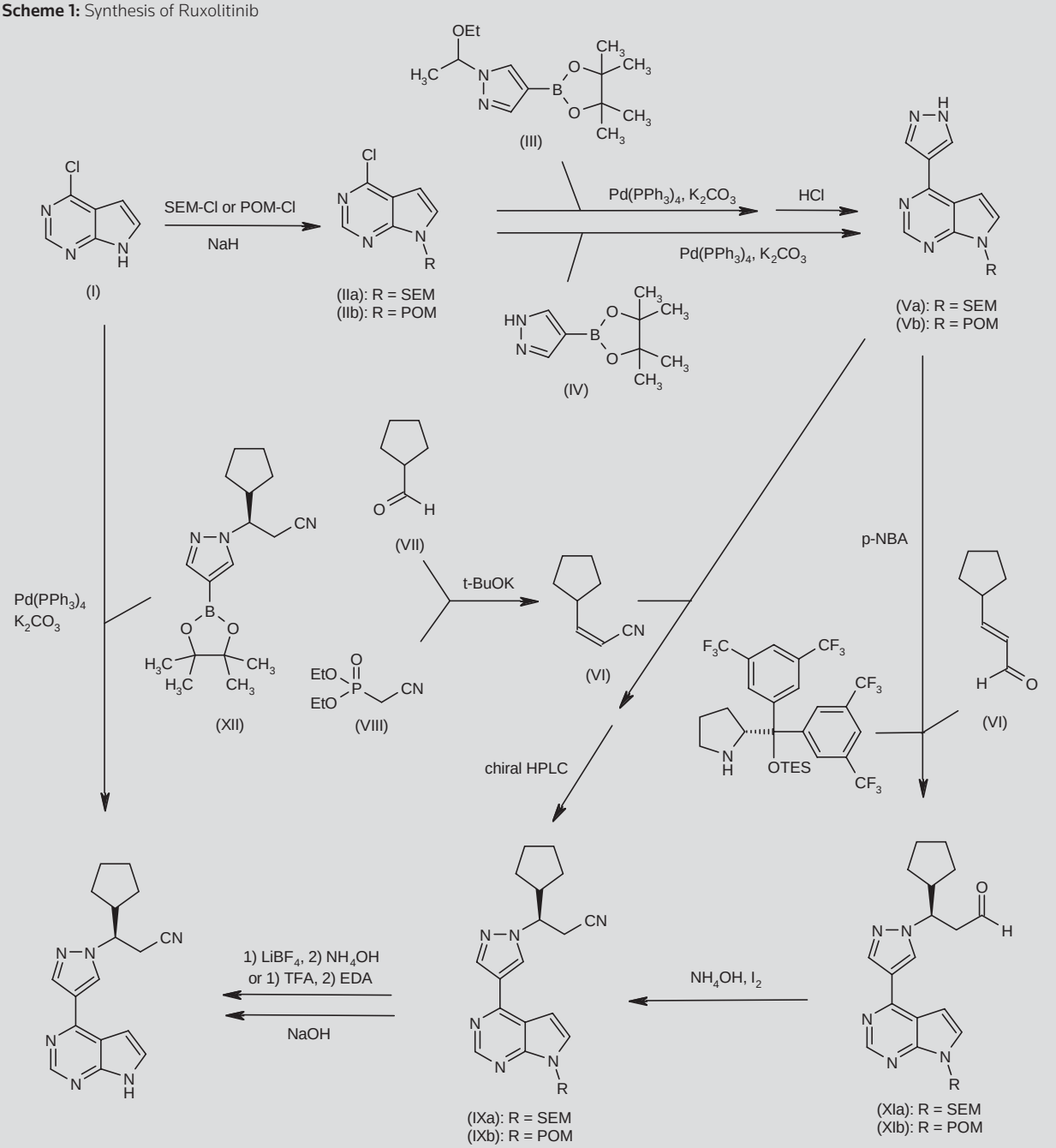
SYNTHESIS*

Ruxolitinib can be synthesized as follows.

N-Protection of 4-chloropyrrolo[2,3-*d*]pyrimidine (I) with either 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) in DMA (1-3) or pivaloyloxymethyl chloride (POM-Cl) in THF (1) in the presence of NaH yields the protected deazapurines (IIa) (1-3) and (IIb) (1), respectively, which by Suzuki coupling with pinacol 1-(1-ethoxyethyl)-4-pyrazolylboronate (III) by means of $Pd(PPh_3)_4$ and K_2CO_3, followed by acidic hydrolysis of the ethoxyethyl group, affords the respective pyrazolyl deazapurines (Va) and (Vb) (1). Alternatively, intermediate (Va) can be obtained by Suzuki coupling of deazapurine (IIa) with unprotected pyrazolylboronate (IV) by means of $Pd(PPh_3)_4$ and K_2CO_3 in DMF/H_2O at 125 °C (2, 3). Michael addition of pyrazole derivative (Va) to 3-cyclopentylacrylonitrile (VI) (obtained by Wittig condensation of cyclopentylcarboxaldehyde [VII] with diethyl cyanomethylphosphonate [VIII] by means of *t*-BuOK in THF) in the presence of DBU in acetonitrile, followed by resolution using chiral preparative HPLC, provides the desired (*R*)-adduct (IXa) (2-4). Alternatively, in an enantioselective procedure, asymmetric aza-Michael reaction of (Va) or (Vb) with (*E*)-3-cyclopentylacrylaldehyde (X) in the presence of *p*-nitrobenzoic acid (*p*-NBA) and a chiral diarylprolinol silyl ether in $CHCl_3$ gives aldehydes (XIa) and (XIb), which by subsequent condensation with NH_4OH, followed by oxidation of the intermediate imines with I_2 in aqueous solution, leads to the corresponding nitriles (IXa) and (IXb) (1). Finally, ruxolitinib is obtained by deprotection of compound (IXa) by sequential treatment with $LiBF_4$ in refluxing acetonitrile/H_2O followed by aqueous NH_4OH (1), or with TFA in CH_2Cl_2 and subsequent basification of obtained TFA salt with ethylenediamine (EDA) in MeOH (2-4), or by deprotection of compound (IXb) by treatment with NaOH in $MeOH/H_2O$ (1). Scheme 1.

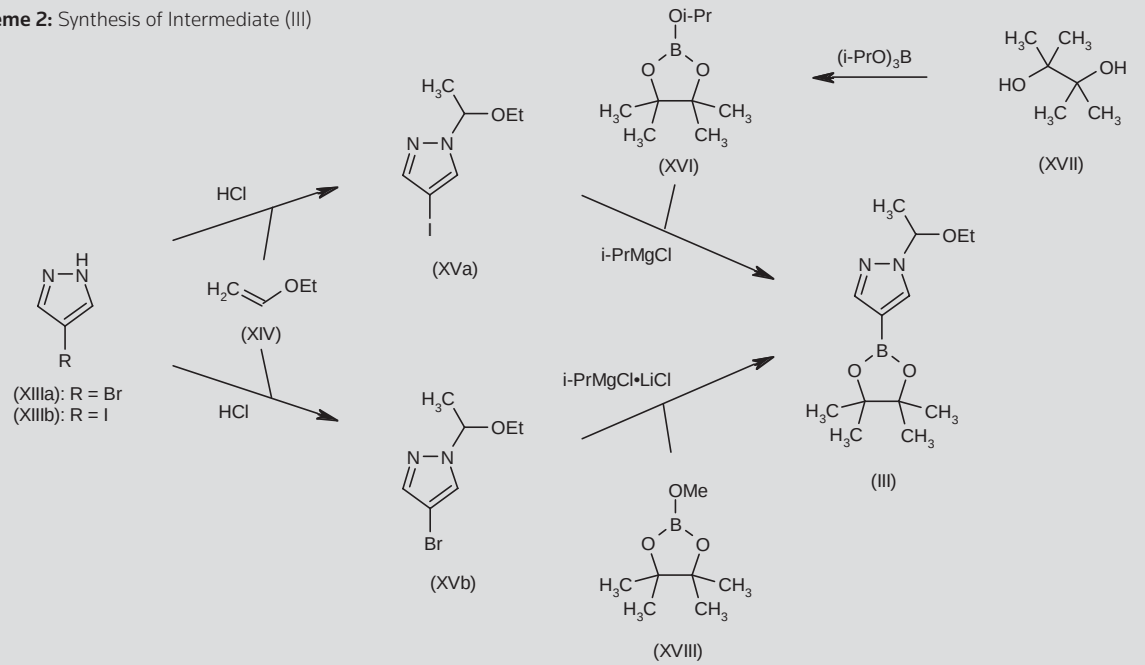
Scheme 1: Synthesis of Ruxolitinib



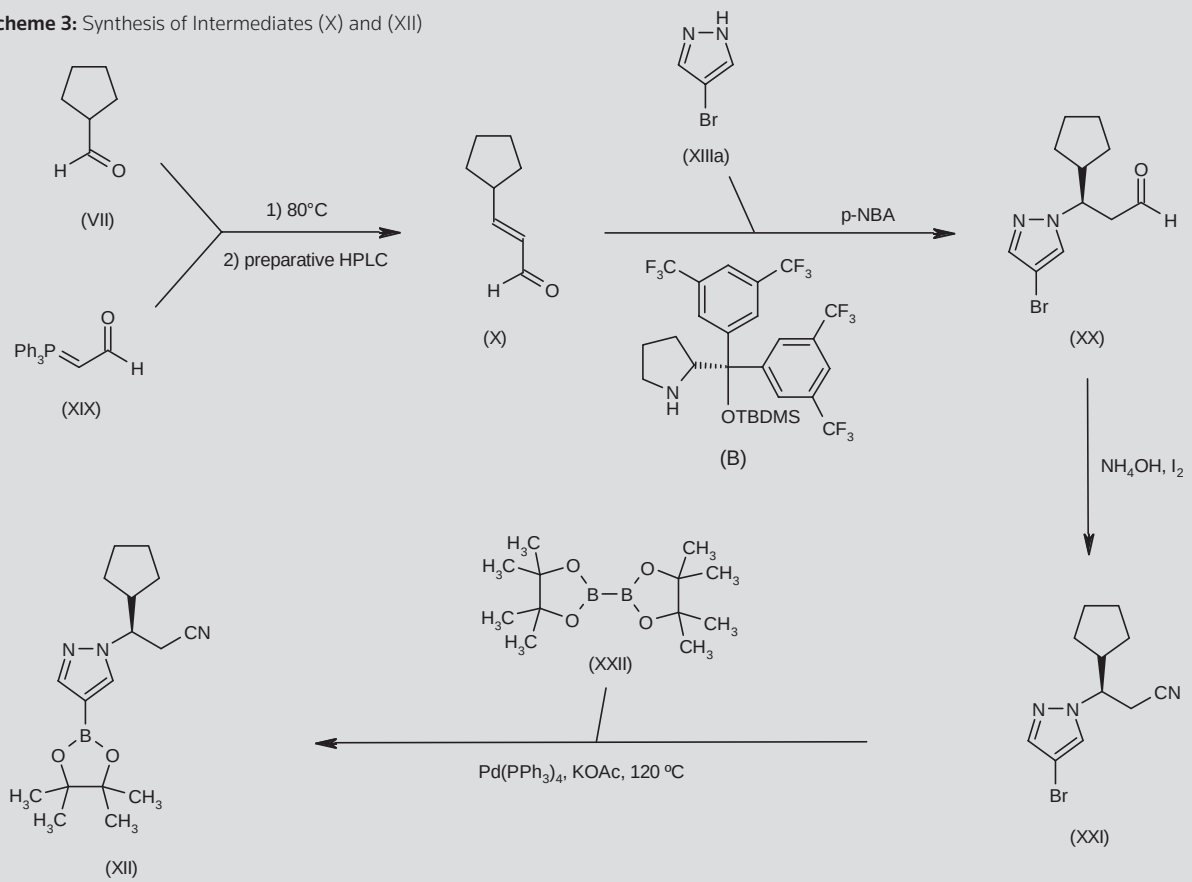
In an alternative strategy, ruxolitinib can be directly obtained by Suzuki coupling of unprotected 4-chloropyrrolo[2,3-*d*]pyrimidine (I) with the pyrazolylboronate (XII) in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in 1,4-dioxane/H_2O at 100 °C (1). Scheme 1.

Intermediate (III) is prepared by protection of either 4-iodopyrazole (XIIIa) or 4-bromopyrazole (XIIIb) with ethyl vinyl ether (XIV) by means of HCl in toluene or CH_2Cl_2 to give the corresponding (1-ethoxyethyl)pyrazoles (XVa) and (XVb). Finally, pyrazole (XVa) is submitted to metal-halogen exchange by means of *i*-PrMgCl in THF, followed by condensation with isopropyl pinacol borate (XVI) (obtained by reaction of pinacol [XVII] with triisopropyl borate at reflux), or pyrazole (XVb) is condensed with methyl

Scheme 2: Synthesis of Intermediate (III)



Scheme 3: Synthesis of Intermediates (X) and (XII)



pinacol borate (XVIII) by means of *i*-PrMgCl·LiCl in THF (1). Scheme 2.

Intermediates (X) and (XII) are prepared by Wittig olefination of cyclopentylcarboxaldehyde (VII) with (triphenylphosphoranylidene)-acetaldehyde (XIX) in benzene at 80 °C, followed by preparative HPLC separation to yield (*E*)-3-cyclopentylacrylaldehyde (X), which upon asymmetric aza-Michael reaction with 4-bromopyrazole (XIIIa) by means of a chiral catalyst and *p*-NBA in THF/H_2O gives the Michael adduct (XX). Then, aldehyde (XX) is treated with NH_4OH and I_2 in 1,4-dioxane/H_2O to give nitrile (XXI), which is finally reacted with bis(pinacolato)diboron (XXII) in the presence of $Pd(PPh_3)_4$ and KOAc in 1,4-dioxane at 120 °C (1). Scheme 3.

BACKGROUND

The Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway plays a critical role in the signaling of a wide array of cytokines and growth factors, leading to various cellular functions, including proliferation, growth, hematopoiesis and immune response (5, 6). The binding of cytokines and growth factors to their corresponding receptors activates JAK, which then phosphorylates the receptor and STAT proteins on specific tyrosine residues. STATs then dimerize, translocate to the nucleus, bind to the consensus DNA sequence of 5′-TT(N4–6)AA-3′ and initiate the transcription of target genes (5, 7, 8).

Four JAK family kinases, JAK1, JAK2, JAK3 and TYK2, and seven STAT family members, STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6, have been identified in mammals. JAK1, JAK2 and TYK2 appear to be ubiquitously expressed, while JAK3 expression is normally limited to lymphoid cells. The JAKs are structurally unique in having a *C*-terminal kinase domain preceded by a pseudokinase domain, which lacks the catalytic activity but has a critical regulatory function. JAKs also have an Src homology 2 (SH2) domain and an *N*-terminal FERM (F for 4.1 protein, E for ezrin, R for radixin and M for moesin) domain that is critical for mediating the association with cytokine receptors. STAT proteins contain an SH2 domain for dimerization and a DNA-binding domain. The amino acid sequence diversity and their tissue-specific distributions account for the diverse roles of STATs in response to extracellular cytokines (5, 7, 8).

The JAK/STAT signal transduction pathways are upregulated by a vast array of cytokines and growth factors and they are also downregulated physiologically. One mechanism for negative regulation of JAK/STAT pathways is through suppressor of cytokine signaling (SOCS) proteins, which directly bind to and inactivate JAKs (9). Also, protein inhibitors of activated STATs (PIAS) bind to phosphorylated STAT dimers, preventing DNA binding, and the SH2-containing phosphatase (SHP-1) (10).

The JAK/STAT pathway mediates signaling by cytokines, which control the survival, proliferation and differentiation of several cell types. Constitutive JAK activation leads to persistent activation of STAT transcription factors, and several cancers exhibit constitutive STAT activation in the absence of JAK or STAT activating mutations. Abnormal constitutive activation of JAK/STAT pathways has been implicated in various cancers and immune disorders (7).

A unique somatic mutation in JAK2 was identified in the majority of patients with myeloproliferative neoplasms. This mutation, encoding a V617F substitution in JAK2, promotes JAK2 catalytic activation and cytokine-independent signaling. JAK2 and JAK3 mutations have also been identified in a minority of polycythemia vera and acute megakaryoblastic leukemia patients (6, 7). STAT3 is persistently activated in many tumors, including major carcinomas and some hematological tumors (11), and TEL-JAK2 fusion due to chromosomal translocation was identified in a small set of human T-cell acute lymphoblastic leukemia (ALL) patients (12). In fact, it is predicted that further JAK/STAT mutations will be identified in cancer. Inhibitors of JAK/STAT pathways are currently under development in the areas of oncology and immune disorders.

Myeloproliferative neoplasms (MPNs; formerly known as chronic myeloproliferative disorders) are clonal hematopoietic stem cell disorders characterized by abnormal proliferation and survival of one or more myeloid cell types in the bone marrow and increased numbers of mature and immature cells in the peripheral blood. They are related to, and may evolve into, myelodysplastic syndrome and acute myeloid leukemia (AML), although MPNs have a much better prognosis than these conditions (13). The current 2008 World Health Organization (WHO) system recognizes eight types of MPNs: chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), polycythemia vera (PV), primary or idiopathic myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukemia (CEL), mastocytosis and unclassifiable myeloproliferative neoplasm (13, 14). In 2005, a somatic activating mutation in the JAK2 non-receptor tyrosine kinase (JAK2V617F) was identified in most patients with PV and in a significant proportion of patients with ET and PMF. Subsequent studies identified additional mutations in the JAK/STAT pathway in some patients with JAK2V617F-negative MPNs, suggesting that constitutive activation of this signaling pathway is a unifying feature of these disorders (15-18). Exaggerated JAK2 signaling is believed to play a dominant role in PV and ET by driving unchecked differentiation and proliferation of erythrocyte and thrombocyte precursors. The prevalence of the JAK2V617F mutation in the classic Philadelphia chromosome-negative myeloproliferative neoplasms (PV, ET and PMF) has made it a much anticipated target for inhibition. Present in over 90% of patients with PV and approximately 50% of patients with ET and PMF, it has been hoped that targeted inhibition of JAK2V617F would achieve similar disease control as imatinib mesylate has produced in CML (19).

Multiple myeloma (MM) is a clonal plasma cell malignancy that accounts for slightly more than 10% of all hematological cancers (20). JAKs can be aberrantly activated by either mutation, such as the JAK2V617F mutation or epigenetic inactivation of negative regulators. Hypermethylation of SOCS-1/3 and SHP-1 has been found in 63% and 80% of myeloma patients, respectively (21, 22). It has been demonstrated that inhibition of JAK1/2 improves the antitumor activity of two common myeloma therapies, melphalan and bortezomib, in preclinical in vivo models (23). The JAK/STAT signaling pathway has also been implicated in the pathology of other cancers such as prostate cancer (24, 25).

The JAK/STAT signaling pathway also mediates inflammation. Chronic activation of immune responses, mediated by inflammatory mediators and involving effector cells of the innate and acquired immune system, characterizes autoimmune disorders. JAKs and

STATs have been implicated in autoimmune disorders such as psoriasis and rheumatoid arthritis (26).

Ruxolitinib (INCB-018424) is a selective JAK1 and JAK2 inhibitor that acts by blocking the JAK/STAT pathway and is undergoing clinical development as an oral formulation for the treatment of several diseases. It is in phase III clinical trials for the treatment of myelofibrosis and is also being evaluated in phase II clinical trials for the treatment of myeloproliferative neoplasms such as advanced PV, ET, post-myeloproliferative disorder AML, psoriasis, prostate cancer and MM. It has been also investigated for the treatment of rheumatoid arthritis.

PRECLINICAL PHARMACOLOGY

Ruxolitinib was identified by Incyte Corporation through an extensive medicinal chemistry effort designed to optimize potency and selectivity for JAK2, as well as pharmaceutical and pharmacokinetic properties (27).

In vitro, ruxolitinib inhibited JAK2 at concentrations below 1 nM and showed more than 500-fold selectivity against a broad sampling of the kinome. It inhibited the proliferation of FDCP and BaF/3 cells expressing the mutated form JAK2V617F, with an IC_{50} of 100-130 nM, but not the proliferation of cell lines expressing activating mutations in either BCR/ABL or c-Kit. The effect of ruxolitinib on cell proliferation correlated well with reduced levels of phosphorylated JAK2 and STAT5 in the BaF/3 cell model, suggesting that the effect was mediated by pharmacological inhibition of the JAK/STAT pathway. Interestingly, the activation of endogenous wild-type JAKs by the addition of IL-3 shifted the potency of ruxolitinib in the BaF/3 model > 5-fold, suggesting that cells expressing the mutated form of JAK2 were more sensitive to ruxolitinib (27).

In colony-forming assays conducted in cells harvested from patients with JAK2V617F-positive PV ruxolitinib inhibited the cytokine-independent formation of erythroid progenitor colonies with an IC_{50} of 67 nM, while normal colony formation from healthy donors was inhibited 50% at doses above 400 nM. Furthermore, ruxolitinib inhibited the proliferation of PV patient samples following ex vivo expansion of erythroid progenitors in serum-free media with an IC_{50} of 60 nM, similar to that observed in semi-solid media (27).

In a mouse model of MPNs, where implantation of BaF/3 cells expressing JAK2V617F results in rapid organomegaly and reduced survival, the oral administration of ruxolitinib was well tolerated and markedly reduced splenomegaly. In this animal model, selective JAK inhibition eliminated neoplastic cells from the spleen, liver and bone marrow, normalizing the histology of affected organs, and significantly prolonged survival (27).

Aberrant JAK/STAT activation has been also observed consistently in MM. Several JAK inhibitors, including ruxolitinib, were used to treat a number of MM cell lines grown under conditions mimicking the supportive natural environment to explore the potential of selective JAK inhibition in controlling the growth and survival of MM cells. This study showed that potent and selective JAK inhibitors ablate STAT phosphorylation in MM cell lines. In addition, a study conducted in a human tumor xenograft showed that inhibition of JAK/STAT activity reduced MM tumor cell proliferation and survival, and improved responsiveness to a variety of therapeutics such as bortezomib in vitro and in vivo (28).

PHARMACOKINETICS AND METABOLISM

In vivo absorption, disposition, metabolism and excretion of radiolabeled ruxolitinib have been investigated in preclinical studies.

Tissue distribution was determined in Sprague-Dawley and Long-Evans rats after a single oral dose of [^{14}C]-ruxolitinib by quantitative whole-body autoradiography. Separately, the mass balance and metabolism of ruxolitinib were determined in CByB6F1 hybrid mice, Sprague-Dawley rats and beagle dogs given a single oral (mice, rats and dogs) or i.v. (rats) dose of [^{14}C]-ruxolitinib. Ruxolitinib-derived radioactivity was widely distributed in a similar pattern to the tissues of Sprague-Dawley and Long-Evans rats. t_{max} was observed within 4 h of dosing, with highest concentrations in the gastrointestinal tract, urinary bladder, bile, renal cortex, renal medulla, liver, aorta, adrenal gland, uveal tract and skin. Elimination was complete in most tissues except for low levels of radioactivity in the aorta, skin and liver of Sprague-Dawley rats. In rats, the route and extent of elimination were similar after oral and i.v. administration, with 92% and 87% of the dose, respectively, excreted within 12 h after dosing. Urine, bile and feces accounted for 49-52%, 37% and 12% of the dose in rats, respectively. Elimination was similarly rapid in dogs, with urine and feces accounting for 34-36% and 55-58% of the dose, respectively. In metabolite profiling studies, ruxolitinib constituted < 3% of the radioactivity in mouse and rat excreta and around 15% in dogs, indicating extensive metabolism. In mice and dogs, unchanged drug was the primary component in circulation, while in rats, metabolites predominated. Species differences in metabolite profiles were minor, with circulating and excreted metabolites mainly consisting of hydroxylations, ketones and, in some cases, subsequent *O*-glucuronides. There were minimal gender differences in plasma pharmacokinetics for ruxolitinib in mice and dogs. However, female rats had higher circulating levels of ruxolitinib compared to males, consistent with in vitro data showing extensive metabolism by the male rat-specific isozymes CYP2C11, CYP2C13 and CYP3A2, but not the female-specific isozyme CYP2C12 (29).

Absorption and distribution of ruxolitinib have also been studied following topical administration. In a 28-day open-label study of ruxolitinib cream applied to psoriatic patients, plasma concentrations of ruxolitinib evaluated at steady state showed continued absorption over the dosing interval, but no correlation to the body surface area treated (30).

SAFETY

Ruxolitinib has been investigated in several clinical studies in patients with primary and secondary myelofibrosis, PV, ET and psoriasis. In these studies, the drug was shown to be well tolerated, with no off-target toxicities.

In a phase I/II study in patients with PMF and post-PV/ET MF, the starting dose of 25 mg p.o. b.i.d. was demonstrated to be the maximum tolerated dose (n = 6 patients). Two patients had grade 4 thrombocytopenia during the first cycle in the 50 mg b.i.d. cohort (n = 5 patients), which defined the dose-limiting toxicity. Myelosuppression was the only toxicity assessed to be related to the drug and this was an on-target effect (31, 32).

In a phase II study in PV patients treated with ruxolitinib 10 mg b.i.d. adverse events of at least grade 2 severity reported in more than 1 patient were anemia (12%) and thrombocytopenia (6%). In the same

study, ET patients were treated with 25 mg b.i.d. and adverse events of at least grade 2 severity reported in more than 1 patient were anemia (18%) and neutropenia (6%) (33). In both PV and ET patients, these adverse events were reversible upon dose interruption or modification.

CLINICAL STUDIES

While PV and ET are managed by phlebotomy and/or cytoreductive therapies such as hydroxyurea and anagrelide in the majority of patients, patients who fail these treatments have limited therapeutic options. Ruxolitinib was evaluated for clinical activity in advanced PV (n = 34) and ET (n = 39) patients refractory to or intolerant of treatment with hydroxyurea in a phase II trial (33). Following an initial phase in which three dose regimens –10 mg b.i.d., 25 mg b.i.d. and 50 mg once a day– were evaluated in each patient population, starting doses of 10 mg b.i.d. in PV patients and 25 mg b.i.d. in ET patients were chosen based on efficacy and tolerability to explore in an expansion cohort. Thirty-four PV patients completed 3 months of treatment and 20 completed 6 months of treatment, and 94% of patients achieved partial or complete response. Over 75% of patients had at least two of the three hematological parameters measured (hematocrit, platelets and white blood cell counts) within the normal range versus 38% of patients at baseline. Twenty-four patients were phlebotomy-dependent in the 6 months prior to study; all became phlebotomy-independent within 2 weeks of initiating ruxolitinib. Twenty-one patients had palpable splenomegaly at baseline and 60% experienced a 50% reduction in spleen size in the first month, which was sustained over the duration of treatment. In 57% of patients with splenomegaly, spleens became nonpalpable. All patients with pruritus (n = 26) experienced rapid, statistically significant and sustained improvement. Marked improvement was noted in bone pain, night sweats and fever. Thirty-nine ET patients completed 3 months of treatment, 17 patients completed 6 months of treatment and 3 patients discontinued, and 61% of patients achieved partial or complete response. Over 50% of patients had at least two of the three hematological parameters within the normal range. Of four patients with splenomegaly, all had a reduction of at least 50% in spleen size. Marked improvement was noted in bone pain, pruritus, weakness, night sweats and abnormal finger sensations.

MF is characterized by progressive bone marrow dysfunction, extramedullary hematopoiesis and massive splenomegaly, elevated levels of inflammatory cytokines, severe constitutional symptoms, cachexia and premature death. Treatment with ruxolitinib resulted in clinical activity in PMF and post-PV/ET MF in a phase I/II clinical trial, showing that clinical improvement occurred regardless of JAK2V617F mutation status or prior MPN diagnosis (31, 32). Over 100 patients were enrolled in the study, with a mean exposure to drug of more than 5 months. Ruxolitinib was associated with a rapid reduction of splenomegaly in over 93% of patients, with a 50% or greater reduction being observed in 35% of patients dosed with 10 mg b.i.d. or 50 mg once daily, and in 59% of patients dosed with 25 mg b.i.d. These declines nearly always occurred within the first month of therapy, with further, slower decreases often observed thereafter. In responding patients, spleen size reduction persisted for the duration of therapy. Constitutional symptoms were reported with high frequency in the study population: night sweats, pruritus and fatigue were reported by > 60%, > 45% and > 90% of patients, respectively. Improvements in self-assessed symptom scores (mean improvement of 40-60%) occurred by the first assessment at week 2. Activity limitations were also reported by a high proportion of MF patients and 70% of respondents reported impaired ability to exercise or get around. Ruxolitinib therapy was associated with rapid and marked improvement in self-assessed score. There was a dose-dependent weight gain, most pronounced in patients with the lowest body mass index values at baseline (34). Profound reductions in inflammatory cytokines were observed by the first evaluation at week 2 in virtually all patients and were maintained during therapy (35), suggesting that cytokine modulation through JAK/STAT inhibition is a potential mechanism of action for ruxolitinib in MF. In these MF patients, the percentage of mutant JAK2V617F relative to wild-type JAK2 was determined in peripheral blood and bone marrow. An excellent correlation in the JAK2V617F allele burden between samples obtained from bone marrow and peripheral blood was observed, indicating that the fraction of cells bearing the mutant clone remains stable during hematopoiesis in this patient group. Despite profound clinical improvements in these patients, JAK2V617F allele burdens did not change dramatically, suggesting that the clinical activity of ruxolitinib might involve inhibition of downstream signaling in cells harboring activating JAK2 mutations rather than changing the allele burden (36).

MF is associated with cachexia and weight loss. These clinical signs, resulting from both hypercatabolism (secondary to increased proinflammatory cytokines) and MF-associated splenomegaly, are associated with decreased survival. Thirty-four symptomatic patients with MF enrolled in the previously described phase I/II were analyzed for the impact of therapy on nutritional status and cachexia. Specifically, patients were assessed for changes in body mass index, serum cholesterol values, spleen size and patient reports of early satiety and anorexia. Additionally, leptin, an adipose-derived protein hormone that plays a key role in regulating energy balance and circulates at levels proportional to body fat in health and disease, was assessed serially. This analysis showed that therapy with ruxolitinib improved the nutritional status of MF patients, including improving pathological weight loss, hypercatabolism-associated hypocholesterolemia and pathologically decreased serum leptin (37).

Two phase III clinical studies, COMFORT-I and COMFORT-II, are being conducted with ruxolitinib. COMFORT-I and -II are enrolling patients diagnosed with MF, either primary MF or post-PV/ET MF, regardless of the presence or absence of the JAK2V617F mutation. In both studies, patients not randomized to receive ruxolitinib will have the opportunity to cross over to receive this investigational therapy (38, 39).

Ruxolitinib has also been investigated in clinical studies in relapsed and refractory leukemias. Patients with AML following prior MPD (sAML) respond poorly to standard cytotoxic chemotherapy and have a poor outcome. Nine patients with de novo AML, three with sAML, two with ALL, one with MPN, two with chronic myelomonocytic leukemia (CMML) and one with CML, were treated with ruxolitinib given orally at 25 mg b.i.d. daily for 4 weeks (cycle 1). Response was assessed after two cycles of treatment and responding patients or patients with stable disease were allowed to continue until progression. Five patients (one with AML, two with sAML and three with

CMML) had the JAK2V617F mutation. Cytogenetic abnormalities included diploid in seven, chromosome 5 and 7 in five, t(2;9) in one and the Philadelphia chromosome in two patients. Patients received a median of one cycle of ruxolitinib (range: one to five cycles), with eight patients having stable disease (three for two cycles, two for three cycles, one for four cycles and two for five cycles). Three patients (including two with sAML and one with CMML, all with JAK2 mutation) had significant declines in their bone marrow blasts (to < 5%) associated with a significant decrease in the size of the spleen and clinical improvement (40).

Ruxolitinib is currently in phase II clinical studies for the treatment of relapsed/refractory AML, ALL and myelodysplasic syndrome, and blast-phase or tyrosine kinase-refractory CML (41). Ruxolitinib is also being investigated in a phase II clinical trial for the treatment of metastatic prostate cancer (42) and in relapsed/refractory MM patients (43).

JAKs are involved in signal transduction from a variety of cytokines involved in the pathogenesis of psoriasis, including IL-12, IL-23 and interferon gamma (IFN-γ). Inhibition of many of those cytokines has demonstrated efficacy in the treatment of psoriasis (26).

Two 28-day studies were performed with ruxolitinib in psoriatic patients. The first study was a double-blind trial conducted in patients with stable plaque psoriasis. Topical ruxolitinib cream was safe and well tolerated at all doses tested and significantly improved overall total lesion score and each component of the total lesion score (thickness, erythema and scaling) as compared to vehicle. In this trial, ruxolitinib 1.5% twice daily also showed improvements in total lesion scores that were similar to the currently approved therapies calcipotriol and betamethasone dipropionate. The second study was an open-label evaluation of the safety, tolerability, efficacy and pharmacokinetics of ruxolitinib cream applied to patients with increasing body surface area involvement. In this study, safety and efficacy were demonstrated with the 1.5% cream b.i.d. at 2-13% body surface area. Improvements in lesion thickness, erythema and scaling, and reduction in treated lesion area were observed in comparison to the untreated lesions. Mean lesion scores for treated areas decreased by 55-61%, while untreated lesions showed a mean change of 14-21%. Mean total area decreased by 59% for treated lesions as compared to 3% for untreated lesions. Efficacy was seen as early as 1 week following study drug application in some patients. Transcriptome and qPCR analysis of skin biopsies indicated that a number of proinflammatory cytokines were downmodulated by ruxolitinib (44). A phase IIb clinical study has been completed with ruxolitinib in psoriatic patients (45) but results are not available yet.

JAKs are involved in signal transduction from a variety of cytokines implicated in the pathogenesis of rheumatoid arthritis (RA), including IL-6, IL-12, I-15, IL-23, granulocyte–macrophage colony-stimulating factor (GM-CSF) and IFN-γ. Inhibition of many of these cytokines has demonstrated efficacy in the treatment of this condition (26, 46).

Since ruxolitinib had shown excellent efficacy in several preclinical models of arthritis, a clinical study was conducted to characterize its efficacy and safety in patients with active RA. Patients with active RA were administered different oral doses of ruxolitinib or placebo for 28 days. Subjects were enrolled into two cohorts, the first cohort at 15 mg b.i.d. or placebo (3:1) and the second cohort at three different doses of 5 mg b.i.d., 25 mg b.i.d. and 50 mg once daily or placebo (3:1 at each dose). Results from the first cohort showed that ruxolitinib was safe and well tolerated at 15 mg b.i.d. and demonstrated preliminary efficacy in the treatment of RA. Analysis of plasma markers indicated that a number of inflammation-associated markers, such as IL-6 and CD40L, were significantly reduced in patients receiving ruxolitinib (47, 48).

The development of ruxolitinib in RA has been discontinued since Incyte Corporation has a novel compound, INCB-28050, which appears to be as effective as ruxolitinib and may offer some potential dosing advantages (source: Medtrack). INCB-28050 is currently completing phase I development (49).

DRUG INTERACTIONS

Two clinical studies have been conducted to evaluate the effects of the inhibition and activation of cytochrome P450 CYP3A4 on the pharmacokinetics and pharmacodynamics of ruxolitinib (50, 51). First, ketoconazole and erythromycin, potent and moderate inhibitors of CYP3A4, respectively, were studied. With ketoconazole coadministration, ruxolitinib C_{max} and AUC increased by 132% and 193%, respectively, and the mean ruxolitinib terminal elimination half-life increased from 3.7 h to 6 h, suggesting that the observed increase in AUC was largely a result of a reduced systemic clearance of the drug. The concomitant use of erythromycin resulted in a less pronounced interaction effect. Ruxolitinib pharmacodynamics, measured as inhibition of IL-6-stimulated STAT3 phosphorylation in whole blood, paralleled the pharmacokinetic profiles of the combinations. These results suggested that ruxolitinib doses should be reduced by 50% when a potent CYP3A4 inhibitor such as ketoconazole is coadministered, and that no change in ruxolitinib dosing regimen is needed when a moderate CYP3A4 such as erythromycin is concomitantly used (50). Secondly, a clinical study was conducted to evaluate the effect of rifampin, a potent inducer of CYP3A4, on the pharmacokinetics and pharmacodynamics of ruxolitinib. Rifampin treatment decreased ruxolitinib C_{max} and AUC by 52% and 71% respectively, while the mean terminal elimination half-life decreased from 3.3 h to 1.7 h, indicating a significant increase in the metabolic clearance of ruxolitinib. However, the observed inhibition of IL-6-stimulated STAT3 phosphorylation in whole blood showed no significant change with rifampin treatment. This apparent discrepancy in the pharmacokinetic/pharmacodynamic data was likely due to an increase in the contribution from ruxolitinib metabolites to its activity. These results are also consistent with in vitro data generated with different metabolites of ruxolitinib that show STAT3-inhibitory activity for these metabolites equivalent to the parent molecule. These results suggested that dose adjustment is not required with concurrent use of drug products that are potent CYP3A4 inducers (51).

SOURCE

Incyte Corp. (US); licensed to Novartis for outside the U.S.

DISCLOSURES

The author states no conflicts of interest.

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