Fedratinib: A Review of Its Pharmacology and Clinical Use

ABSTRACT

Fedratinib (INREBIC®) is a JAK2-selective inhibitor that has been developed as an oral treatment for myelofibrosis. It was approved for the first time in the United States in August 2019 to treat adult patients with intermediate-2 or high-risk primary or secondary (post-polycythaemia vera or post-essential thrombocythemia) myelofibrosis. Fedratinib is an anilinopyrimidine derivative and is metabolized by CYP3A4, CYP2C19 and flavin-containing monooxygenase-3. Fedratinib is mainly excreted in faeces, and the effective half-life is 41 hours. The recommended dosage is 400 mg once daily (with or without food. The dosage should be reduced to 200 mg once daily in patients receiving CYP3A4 inhibitors and in patients with severe renal impairment. Fedratinib's recent approval adds to the few therapeutic option choices available to individuals with MF. The most common adverse events were mild gastrointestinal toxicities. Fedratinib comes with a boxed warning about the risk of serious and potentially deadly encephalopathies, such as Wernicke's.

Keywords: Fedratinib, CYP3A4 inhibitors, encephalopathies, gastrointestinal toxicities

INTRODUCTION

Fedratinib is an oral kinase inhibitor that inhibits JAK2 and FMS-like tyrosine kinase 3 in both wild type and mutationally activated forms (FLT3). The US Food and Drug Administration (FDA) approved it for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-PV or post-ET) MF in August 2019.[1] Fedratinib (SAR302503/TG101348) is a JAK2-selective inhibitor that has shown therapeutic effect in MF patients in early-phase studies. It appears to have activity against a broader family of kinases and kinase mutants.[2,3] Fedratinib has a modest inhibitory effect on JAK1, JAK3 and tyrosine kinase 2 (TYK2). [4] JAK1, JAK2, JAK3, and TYK2 are members of the Janus kinase

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(JAK) family of protein-tyrosine kinases.[5] Fedratinib is an inhibitor of several cytochrome P450 (CYP)enzymes and is a weak inhibitor of CYP2D6 and a moderate inhibitor of CYP2C19, CYP3A4.[6] Fedratinib binds to both the ATP-binding site and the substrate-binding site.[7] Fedratinib was recently included to the National Comprehensive Care Network's MPN treatment guidelines as an initial therapy option for patients with intermedicate-2 or high-risk MF or as second-line therapy for those who do not react to ruxolitinib or lose their response.[8] In patients with MF, the highest tolerable dose of fedratinib was established to be 680 mg once daily (QD), and single oral doses of up to 680 mg fedratinib were tolerated by the healthy subjects. Fedratinib solubility is pH dependant; it is easily soluble at pH 1, but almost insoluble at pH 7.4 (112, 30, 0.02 and 0.004 mg/mL at pH 1, 4.5, 6.8, and 7.4, correspondingly). [9]

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Table 1. DEVELOPMENT OF FEDRATINIB

DEVELOPMENT OF FEDRATINIB	2005	JAK2V617F mutation discovered
	2006	Frist synthesis of TG101348(fedratinib)
	2006-2008	Preclinical studies
	2008	Human phase 1 trial open
	2011	JAKARTA trial
	2012	JAKARTA 2 trail
	2013-2017	FDA clinical hold
	2019	FREEDOM, FREEDOM 2 trials
	2019	FDA approval in myelofibrosis

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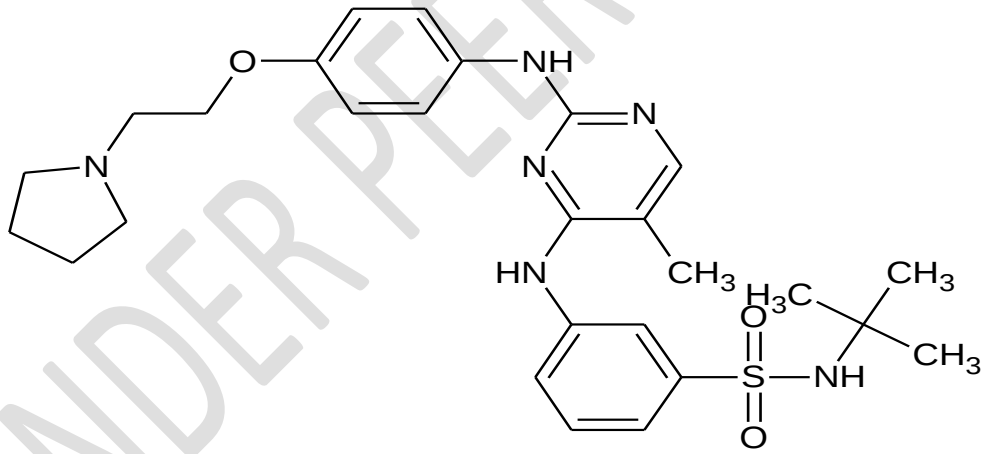
CHEMICAL STRUCTURE AND DEVELOPMENT OF FEDRATINIB

In 2005, the JAK2V617F mutation was discovered, ushering in a new age of rationally planned targeted therapy for MPNs. [10-13] The JAK2V617F mutation, which promotes JAK2 signalling, is the most prevalent somatic mutation in MPNs, and it is disease-causing

and central to the pathogenesis of MPN. [14-15] The therapeutic potential of anoncogenic kinase allele was immediately apparent, and JAK2 inhibitors were produced quickly and put to the test in the clinic. In the year 2011, The FDA authorised ruxolitinib as the first JAK2 inhibitor for treatment of MF, followed by fedratinib approval in 2019.[16] The clinical activity of fedratinib in MF at the recommended beginning dose of 400 mg/day has been evaluated in JAK-inhibitor-naive patients as well as individuals who have previously been treated with other JAK inhibitors(ruxolitinib). [17,18] Fedratinib was discovered after a new series of pyrimidine-based inhibitorsdesigned and optimised utilising rational structure-based approaches to target JAK2. [19,20] Fedratinib is an anilinopyrimidine derivative.[21]

STRUCTURE



IUPAC Name: N-tert-butyl-3-{[5-methyl-2-({4-[2-(pyrrolidin-1-yl) ethoxy] phenyl} amino) pyrimidin-4-yl] amino} benzene-1-sulfonamide

Chemical Formula: $C_{27}H_{36}N_6O_3S$

PHARMACOLOGY

Fedratinib has a quick oral absorption rate, a high protein binding rate (>92 percent bound to protein), a long terminal half-life, and is primarily excreted through the faeces.[22] Mostly processed by Cytochrome (CY)P3A4 in humans; hence, if fedratinib is given concurrently

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with powerful CYP3A4 inhibitors, its plasma levels may rise. Clarithromycin, voriconazole, itraconazole, and grapefruit juice are examples of potential culprit agents and both patients and community physicians should be aware of these potential interactions. If these agents cannot be avoided, dose reduction should be considered to reduce the risk of adverse effects. If the CYP3A4 inhibitor is stopped, dosage should be increased immediately.[23]

JAK2 selectivity

Fedratinib was designed as a JAK2-selective inhibitor with better potency for JAK2 than closely related kinase family members utilising structure-based drug design. It binds to both the ATP and peptide-substrate binding sites in the kinase domain, according to structural modelling, which could explain why there is no hereditary resistance to fedratinib.[24]

FLT3 inhibition

Fedratinib inhibits mutant and wild-type FLT3, a tyrosine kinase found in hematopoietic stem cells and myeloid progenitor cells that play a crucial function in cell survival as well as proliferation. FLT3 activation leads to phosphorylation and activation of the PI3K/AKT, MAPK, and STAT5 signalling pathways, which are involved in mechanisms of anti-apoptosis, proliferation, and differentiation pathways. [25,26]

BRD4 inhibition

Fedratinib inhibits BRD4; fedratinib's dual targeting of JAK2 and bromodomains may contribute to the drug's therapeutic effect. Members of the group family of BET proteins (BRD2, BRD3, BRD4, and BRDT) are linked to a variety of malignancies. [27-30]

PHARMACOKINETICS

The pharmacokinetics and acceptability of single fedratinib dosages ranging from 10 to 680 mg were evaluated in a randomised, placebo-controlled phase I study in healthy volunteers. Drug was quickly absorbed, with peak plasma concentrations occurring 2–3 hours after

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dosing. Fedratinib exposure appeared to grow faster than dosage proportionality would predict, with a threefold increase in exposure in the 80–500 mg dose range compared to dosage proportionality. Similarly, mean steady-state maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC0-t) values increased 54- and 88-fold, respectively, in patients with MF receiving fedratinib dosages of 30–800 mg/day.[31] Fedratinib has a 41-hour effective half-life. By the 15th day of treatment, steady-state plasma concentrations had been attained. Fedratinib is metabolised by cytochrome P450 enzymes (CYP3A4, CYP2C19). Co-administration with CYP3A4 inhibitors (e.g., ketoconazole) can enhance fedratinib exposure (possible drug-drug interactions should be investigated prior to starting treatment).

In healthy volunteers, coadministration of a single dosage of 500 mg with pantoprazole (40 mg once daily) had no effect on fedratinib pharmacokinetics.[32] Fedratinib accounts for around 80% of the circulating drug in plasma after oral administration, with 77 percent of the administered dose (23 percent unaltered) excreted in faeces and 5% (3 percent unchanged) excreted in urine following a single oral dose. With fedratinib, there was no clinically significant influence of age, race, sex, body weight. Fedratinib's pharmacokinetics are unaffected by mild to severe hepatic impairment or minor renal impairment. Moderate (creatinine clearance, 30-59 mL/min) or severe (creatinine clearance, 15-29 mL/min) renal impairment, on the other hand, resulted in increased fedratinib exposure. Dose reductions are required for severe renal impairment.[33] In two Phase I studies in healthy male subjects, the effect of food intake on the pharmacokinetics (PKs) and tolerability of single-dose fedratinib (FED12258: 100 mg or 500 mg) under fasted or fed [high fat breakfast] conditions; ALI13451: 500 mg under fasted or fed [low or high fat breakfast] conditions was investigated. The area under the plasma concentration—time curve extended to infinity for the 500 mg dosage was 0.96 (100 mg; high fat/fasted), 1.19–1.24 (500 mg; high fat/fasted), and

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1.22 (500 mg; low fat/fasted). Fedratinib 500 mg reached maximal plasma concentration 4 hours after a high fat breakfast and 2–2.5 hours after a low-fat breakfast or when fasting; the terminal half-life was 76–88 hours (fasted) and 73–78 hours (nonfasted) (fed). Food consumption had minimal effect on fedratinib PKs, and the drug's tolerance was enhanced when given after a high-fat breakfast.[34]

Table 2. Absorption and metabolism

Absorption	Peak plasma time: ~3 hr (steady-state) Peak plasma concentration: 1,804 ng/mL AUC: 26,870 ng·hr/mL Steady-state reached within 15 days **Effect of food** • A low-fat, low-calorie or a high-fat, high-calorie meal increased AUC up to 24% and peak plasma concentration up to 14% of a single 500-mg dose
Distribution	Vd (steady-state): 1,770 L Protein bound: ≥92%
Metabolism	Primarily metabolized by CYP3A4, CYP2C19, and flavin-containing monooxygenase 3 (FMO3) Fedratinib accounts for ~80% of total circulating drug in plasma after oral administration

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Elimination	Half-life: ~ 114 hr Clearance: 13 L/hr Excretion: Faeces (77% [23% unchanged]); urine (5% [3% unchanged])

PHARMACODYNAMICS

JAK/STAT signaling

Fedratinib lowered phosphorylation of downstream STAT3/5 proteins (pSTAT3/pSTAT5), slowed cell proliferation, and triggered apoptotic cell death in cell models expressing mutationally active JAK2 or FLT3-ITD. Fedratinib, which inhibits pSTAT5, improved illness-associated characteristics in mice models of JAK2V617F-driven myeloproliferative illness, including reduced white blood cell (WBC) counts, haematocrit, splenomegaly, and reticulin fibrosis.[35] Fedratinib effectively suppressed KITD816V and FIP1L1-PDGFRA in leukemic cell lines, suggesting that the drug may have a function in the treatment of patients with chronic eosinophilic leukaemia.[36] Fedratinib inhibited JAK2/STAT1 signalling, which reduced monosomy 7 myelodysplastic syndrome (MDS) blasts in bone marrow cells suggesting it could be a targeted therapy for monosomy 7 MDS and acute myeloid leukaemia patients.[37]

JAK2V617F

Fedratinib has been shown to be effective against JAK2V617F-expressing cells in animal studies. [38-40] Fedratinib suppressed phosphorylation of STAT3/5, reduced splenomegaly, and

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improved white blood cell counts in mice with JAK2V617F-positive myeloproliferative illness, attenuated myelofibrosis, cell counts and haematocrit, and greater chances of surviving. It reduced cell proliferation and extended survival in a variety of solid tumour models. Concentrations of fedratinib less than 1 mol/L were shown to completely block colony formation in most tumour cell lines.[41] Fedratinib's impact on JAK2V617F allele burden in MF patients is less known.[42]

CLINICAL TRIALS OF FEDRATINIB

Phase I

MF-TG101348-001

NCT00631462

A phase 1, open label, dose escalation study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of orally administered FDR in patients with MF. Objective to evaluate the safety and tolerability of the drug in patients with MF.

Phase II

JAKARTA2

NCT01523171

Adult patients with a current diagnosis of intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythemia, myelofibrosis who were ruxolitinib resistant or intolerant after a minimum of 14 days of therapy were enrolled in this single-arm, open-label, non-randomised, phase 2 multicentre study, which was conducted at 31 sites in nine countries. Palpable splenomegaly (5 cm below the left costal margin), an Eastern Cooperative Oncology Group performance status of 2 or less, and a life expectancy of 6 months or fewer were the other key inclusion criteria. The primary goal of

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this phase 2 research was fulfilled, demonstrating that patients with ruxolitinib-resistant or ruxolitinib-intolerant myelofibrosis might benefit from fedratinib, though at the cost of some possible harm, which has to be investigated further. In the JAKARTA2 trial, there was one instance of grade 3 hepatic encephalopathy, but no verified case of Wernicke's encephalopathy (WE).

Phase III

JAKARTA

NCT01437787

Multicentre, randomized, double-blind, placebo-controlled, 3-armstudy of FDR (400 or 500 mg or placebo) in patients with intermediate-2 or high-risk MF– Primary objective: to evaluate the efficacy of daily oral doses of 400 or500 mg of the drug compared with placebo in the reduction of spleen volume. Secondary objectives: to evaluate the effect on MF-associated, the OS, PFS, durability of spleen response and drug safety. In the United States, regulatory approval of the recommended fedratinib 400 mg daily dosage for the treatment of individuals with intermediate-2 or high-risk MF was based in part on clinical effectiveness and safety in JAKARTA trial.

Phase III

FREEDOM

NCT03755518

(Resistant/intolerant to RUX)

Single-arm, open-label efficacy and safety trial of FDR in subjects with INT or high-risk MF previously treated with RUX. Primary objective to assess subjects gaining ≥35% SVR and a key secondary objective is to evaluate the safety of FDR.

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Phase III

FREEDOM2

NCT03952039

Single-arm, open-label efficacy and safety trial of FDR in subjects with INT or high-risk MF previously treated with RUX. The goal is to compare FDR with BAT in terms of efficacy and safety. The primary goal is to determine the percentage of participants in the FDR and BAT arms who have an SVR of at least 35 percent.

SAFETY

Fedratinib's safety and tolerability were assessed using the treatment-emergent adverse events (TEAEs). Between the first dosage of fedratinib and 30 days following the final dosage, a TEAE was defined as any AE that emerged, worsened, or became severe.[43] In clinical studies eight out of 877 individuals had cases consistent with Wernicke's encephalopathy. As a result, the US Food and Drug Administration (FDA) placed a clinical hold on the development of fedratinib. While the probable cases of Wernicke's encephalopathy (a neurological side effect brought upon by thiamine deficiency) were being investigated in 2013. In August 2017, the US FDA lifted the clinical hold after receiving further safety data.[44,45,46] Fedratinib comes with a boxed warning about the risk of serious and potentially deadly encephalopathies, such as Wernicke's. [47]

The following clinically significant side effects are listed elsewhere in the labelling of fedratinib

- Encephalopathy, including Wernicke’s

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Wernicke's encephalopathy is a neurologic emergency resulting from thiamine (Vitamin B1) deficiency. Signs and symptoms of Wernicke's encephalopathy may include ataxia, mental status changes, and ophthalmoplegia (e.g., nystagmus, diplopia)

- Anemia and Thrombocytopenia
- Gastrointestinal Toxicity
- Hepatic Toxicity
- Amylase and Lipase Elevation

CONCLUSION

Fedratinib is an exciting new treatment option for patients with advanced MF who previously had few therapeutic alternatives. Fedratinib has a longer track record in clinical trials. The possibility of secondary resistance developing during therapy must be determined. Fedratinib therapy significantly reduced symptoms in patients with MF but these benefits were accompanied by toxic effects in some patients, the most important being encephalopathy of unknown mechanism.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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