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JAK inhibitors: need for dosage individualisation?

Jérémie Tachet, Doctoral pharmacy student; Prof. François Girardin, MD, MSc, eMBA

Regional Pharmacovigilance Centre, Clinical Pharmacology Department,
Lausanne University Hospital (CHUV), Switzerland

Janus kinases (JAK) are multi-domain non-receptor tyrosine kinases with pivotal functions in cellular signal transduction and provide unique opportunities in the modulation and long-term control of pathogenic immune response in multiple disease states (1). JAK inhibitors (JAKi) are used for multiple inflammatory and oncological disorders, such as inflammatory bowel diseases, rheumatoid arthritis, immune-mediated arthropathies (e.g. spondyloarthritis), multiple immune-driven dermatological diseases, myeloproliferative neoplasms, polycythaemia vera, essential thrombocythaemia, and more recently graft versus host disease (GvHD). In Switzerland, the first JAKi to be approved were ruxolitinib (Jakavi®, 2012) and tofacitinib (Xeljanz®, 2013).

The type of JAKi affinity to the receptor plays a key role in the drug properties and disease targets in these highly selective medications. All JAKi for chronic inflammatory diseases inhibit, at least partly, the JAK1 isoform: this specific inhibition could be associated with a class effect with respect to their safety (1).

The rapid rate of resynthesis (2–4h) for the isoforms JAK1, JAK2, and TYK2 impacts the spectrum of JAKi characteristics and their duration of action (2). Inhibition of one or more JAK isomers results in a wide range of biological responses (i.e., desired and untoward effects).

The pharmacokinetics of JAKi, such as the biological half-life, peak concentrations, the time to reach the maximum concentration at the target site, and the elimination pathways, as well as the binding type and the affinity to the four isomers, affect their pharmacodynamics. JAKi represent a chemically heterogenous group of medications with various pharmacokinetic and pharmacodynamic patterns of physiological actions: concentration-effect and concentration-adverse drug reaction (ADR) relationships are substance-specific. Efficacy and ADR depend essentially on the concentration-response relationship to adjust the drug dosage and drive concentrations close to target within therapeutic ranges. For instance, an association between plasma exposures and efficacy was observed in ulcerative colitis and rheumatoid arthritis patients treated with upadacitinib. Similar relationships were seen for serious infections, liver transaminase or CPK elevation, lymphopenia, and decrease in haemoglobin (3–5).

Novel mechanisms of immunosuppression inevitably entail a risk of either insufficient efficacy or toxic effects, raising dosage optimisation concerns for a large array of non-standard patients. Safety issues of JAKi (e.g. increase in cardiovascular events, cancers, opportunistic infections, reactivation of herpes zoster, chronic viral hepatitis infections, and latent tuberculosis) are discussed in a separate article in the newsletter.

Formatted standard-of-care to patients with straightforward oral administration is the rule to streamline immunosuppressive treatments, regardless of age, gender, pharmacogenetic profile, drug-drug interactions or disease-induced metabolic phenoconversion (6). Pharmacokinetic characteristics of JAKi and drug-drug interactions may affect the effectiveness and tolerability. In particular, the cytochromes P450 (CYP), whose activity is strongly influenced by genetic polymorphism and drug-drug interactions (induction or inhibition), play a critical role in the biotransformation of JAKi to active metabolites considered as active compounds. Pharmacokinetic characteristics of JAKi are summarised in Table 1.

Table 1. Pharmacological descriptions of the main JAKi available in Switzerland

Molecule	Drug name	Indications	Half-life	Dosage	Pharmacokinetic / DDIs
Abrocitinib	Cibinqo®	• AD • **Clinical studies**: Prurigo nodularis, chronic pruritus, plaque psoriasis	3–5 h	100–200 mg QD	• Elimination: mainly hepatic (<1% renal in unchanged form) • Substrate: CYP2C19 (major), CYP2C9 (major) • Active metabolites (renal elimination)
Baricitinib	Olumiant®	• RA, AD • **Swissmedic, FDA**: COVID-19 • **FDA, EMA**: alopecia areata • **Clinical studies**: SLE, lupus nephritis, type I diabetes, giant cell arteritis, PJIA, Sjögren's syndrome, pyoderma gangrenosum, HIV, dermatomyositis, …	12–16 h	2–4 mg QD	• Elimination: mainly renal (69% renal in unchanged form) • Substrate: CYP3A4, P-gp (minor)
Fedratinib	Inrebic®	• MF • **Clinical studies**: chronic neutrophilic leukaemia, acute myeloid leukaemia, essential thrombocythaemia, chronic beryllium disease	41 h	Depends on the platelet count and adverse effects: • Platelets ≥50 x 109/l :400 mg QD	• Elimination: mainly hepatic (3% renal in unchanged form) • Substrate: CYP3A4 (major) and FMO3. • Inhibits: CYP2C19 (moderate), CYP3A4 (moderate).
Ruxolitinib	Jakavi®	• MF, PV, aGvHD • **EMA, FDA**: cGvHD • **Clinical studies**: AD, vitiligo, CAR-T cell therapy-related cytokine release syndrome, COVID-19, breast cancer, acute lymphoblastic leukaemia, chronic myeloid leukaemia …	3h–5.8h	Depends on the platelet count: • Platelets > 200,000/mm³: ・MF: 20 mg BID ・PV: 10 mg BID • Platelets 100,000-200,000/ mm³ ・MF: 15 mg BID ・PV: 10 mg BID • Platelets 50,000-100,000/mm³ ・MF: max. 10 mg BID ・PV: 5 mg BID	• Elimination: mainly hepatic (<1% renal in unchanged form) • Substrate: CYP3A4 (major) • Active metabolites (renal elimination)

Molecule	Drug name	Indications	Half-life	Dosage	Pharmacokinetic / DDIs
Tofacitinib	Xeljanz®	• RA, PsA, UC • **EMA, FDA**: AS, UC, PJIA • **Clinical studies**: COVID-19, systemic sclerosis, Crohn's disease, alopecia areata, dermatomyositis, psoriasis, SLE, AD, AS, uveitis, sarcoidosis …	3 h	5–10 mg BID	• Elimination: mainly hepatic – 70% (30% renal in unchanged form) • Substrate: CYP3A4 (major)
Upadacitinib	Rinvoq®	• RA, PsA, AS, AD • **EMA, FDA**: UC • **Clinical studies**: Crohn's disease, PJIA, hidradenitis suppurativa, vitiligo, SLE, giant cell arteritis, Takayasu's arteritis	9–14 h	15–45 mg QD	• Elimination: mainly hepatic (24% renal in unchanged form) • Substrate: CYP3A4 (major)

AD, atopic dermatitis; aGvHD, acute graft versus host disease; AS, ankylosing spondylitis; BID, twice a day; CES, carboxylesterase; cGvHD, chronic graft versus host disease; CYP, cytochrome P450; DVT, deep vein thrombosis; FMO, Flavin-containing monooxygenase; GI, gastrointestinal; MACE, major adverse cardiovascular events; MF, myelofibrosis; PE, pulmonary embolism; P-gp, P glycoprotein; PJIA, polyarticular juvenile idiopathic arthritis; PV, polycythaemia vera; PsA, psoriatic arthritis; QD, once a day; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; UC, ulcerative colitis. **Table adapted from Tachet Revue Médicale Suisse, 2022** (7).

The drug actionability is enhanced by using different doses for different indications in a wide range of diseases in rheumatology, dermatology, haematology, infectiology, and immunology (Table 1). Recently, tofacitinib, filgotinib or upadacitinib indications have been extended to include gastroenterology for inflammatory bowel diseases. In clinical trials, Crohn's disease patients treated with upadacitinib were within off-label indications, with a tripling of the dose for the induction phase (45 mg/d) and a doubling of the dose for the maintenance phase (30 mg/d) compared to the dose administered for e.g. rheumatoid arthritis or atopic dermatitis (15 mg/d) (8, 9). However, tofacitinib and filgotinib (approved in the EU but not in Switzerland) dosages were not sufficiently high and failed in pivotal clinical trials for the treatment of Crohn's disease (phase 3), in contrast to ulcerative colitis, which requires lower doses (10 mg BID and 200 mg/day, respectively, in induction therapy) (10, 11). The difference in optimal doses between these patient populations with IBD is related to the difference in the exposure-response relationship and the expected risk-benefit trade-off (5).

Considering the inhomogeneous pharmacokinetic characteristics and the variations in dosage that significantly impact biological effects, JAKi are drug candidates that would require individual dose adjustment to optimise their effectiveness and safety profiles. Thus, dose-dependent efficacy and tolerability issues could be addressed by treatment individualisation approaches, such as therapeutic drug monitoring (TDM), using blood concentration as a marker for drug exposure-response optimisation (12).

In summary, JAKi are subject to a wide range of intrinsic and extrinsic factors (e.g. drug-drug interactions, patient characteristics, including pharmacogenetic profile) that influence their disease-specific efficacy and tolerability. Recently, clinical trials have provided new relevant information on

the crucial role of concentration-response relationships to balance the expected risk-benefit ratios. Using therapeutic drug monitoring for treatment individualisation, concentration-effect and concentration-tolerability relationships could constitute a new clinical marker to gain insight into the effectiveness and safety issues of JAKi.

References

(1) Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther. 2021;6(1):402.

(2) Eichner A, Wohlrab J. Pharmacology of inhibitors of Janus kinases – Part 2: Pharmacodynamics. JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2022;20(12):1621-31.

(3) Muensterman E, Engelhardt B, Gopalakrishnan S, Anderson JK, Mohamed MF. Upadacitinib pharmacokinetics and exposure-response analyses of efficacy and safety in psoriatic arthritis patients - Analyses of phase III clinical trials. (1752-8062 (Electronic)).

(4) Nader A, Mohamed M-EF, Winzenborg I, Doelger E, Noertersheuser P, Pangan AL, et al. Exposure–Response Analyses of Upadacitinib Efficacy and Safety in Phase II and III Studies to Support Benefit–Risk Assessment in Rheumatoid Arthritis. Clinical Pharmacology & Therapeutics. 2020;107(4):994-1003.

(5) Ponce-Bobadilla AV, Stodtmann S, Eckert D, Zhou W, Liu W, Mohamed MA-O. Upadacitinib Population Pharmacokinetics and Exposure-Response Relationships in Ulcerative Colitis Patients. (1179-1926 (Electronic)).

(6) Ing Lorenzini K, Desmeules J, Rollason V, Bertin S, Besson M, Daali Y, et al. CYP450 Genotype—Phenotype Concordance Using the Geneva Micrococktail in a Clinical Setting. Front Pharmacol. 2021;12.

(7) Tachet J, Dumusc A, Conrad C, Grandoni F, Chalandon Y, Ribi C, et al. Janus kinase inhibitors: new perspectives for precision medicine? Revue Médicale Suisse. 2022;8(800):1979-83.

(8) Traboulsi C, Ayoub F, Silfen A, Rodriguez TG, Rubin DT. Upadacitinib Is Safe and Effective for Crohn's Disease: Real-World Data from a Tertiary Center. Digestive Diseases and Sciences. 2023;68(2):385-8.

(9) Barberio B, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. Gut. 2023;72(2):264.

(10) Panés J, Sandborn WJ, Schreiber S, Sands BE, Vermeire S, D'Haens G, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. (1468-3288 (Electronic)).

(11) Vermeire S, Schreiber S, Petryka R, Kuehbacher T, Hebuterne X, Roblin X, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. The Lancet. 2017;389(10066):266-75.

(12) Buclin T, Thoma Y, Widmer N, André P, Guidi M, Csajka C, et al. The Steps to Therapeutic Drug Monitoring: A Structured Approach Illustrated With Imatinib. Front Pharmacol. 2020;11:177.