Patients with chronic inflammatory diseases can experience higher exposure of small-molecule drugs than healthy volunteers: A population PK model-focused analysis of recently approved drugs

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CONCLUSION

Based on PopPK model parameters, 26% (5 of 19) of small-molecule drugs approved for chronic inflammatory diseases between 2010 and 2024 show meaningful PK difference between patients and healthy volunteers (>20% lower CL/F = 1.25x AUC)

Variable PK differences of small-molecule drugs in chronic inflammation vs. healthy ranging from no significant change to approximately 50% lower CL/F can be expected

Overall, chronic inflammation may be a potential influential factor on the PK of small-molecule drugs and should be taken into consideration in translating dose predictions from HVs to patients

Extensively metabolized (primarily by CYP3A4 or CYP2C19) and potentially medium bioavailability (60% – 80%) drugs show the largest decrease in CL/F

MOTIVATION

- Many small-molecule drugs are mainly metabolized by CYP enzymes
- Chronic inflammation has long been known to down-regulate the CYP-mediated metabolism of small-molecule drugs [1,2]
- Higher exposures in patients can complicate dose translation from HVs
- To our knowledge, no review of the impact of chronic inflammation on patient exposure of small-molecule drugs exists

OBJECTIVES

- Quantify the higher exposure of recently approved small-molecule drugs in patients with chronic inflammatory diseases compared to HVs based on available information
- Identify potential causes for the higher exposure
- Complement the recent review of lower patient exposures of therapeutic proteins under chronic inflammation [3]

METHODS

We searched the Drugs@FDA database [4] for new drug applications (NDAs) of "Type 1: new molecular entity" (NME) between 01/2010 and 12/2024 for small-molecule drugs indicated for the chronic inflammatory diseases:

- Rheumatoid Arthritis (RA)
- Psoriasis (PsO)
- Psoriatic Arthritis (PsA)
- Ulcerative Colitis (UC)
- Crohn's Disease (CD)
- Multiple Sclerosis (MS)
- Atopic Dermatitis (AD)
- Biliary Cholangitis (BC)
- Any type of Vasculitis

We located either the "Clinical Pharmacology Review", "Multi-Discipline Review", or "Integrated Review" depending on the type of the NDA. We reviewed the section "General Pharmacology and Pharmacokinetic Characteristics" for a discussed difference in PK between patients and healthy volunteers (HVs) and the "Population PK Analysis" review for PopPK model parameters and disease-specific covariates. We further reviewed the labels for information on the bioavailability, metabolic pathways and fraction of unchanged drug recovered in urine and feces.

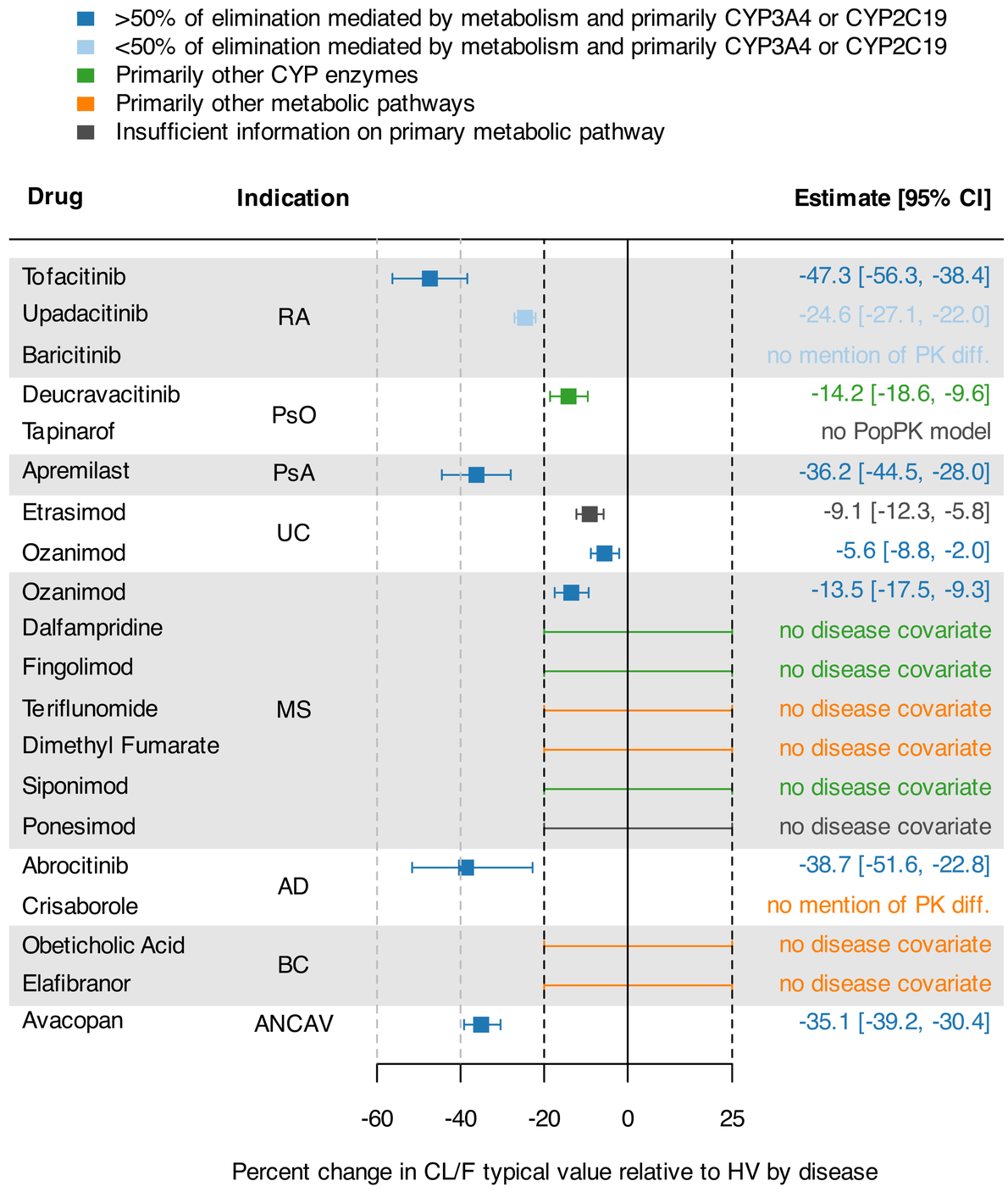
We focused on PopPK model parameters to obtain precise estimates of the actual disease-related effect. We did not analyze estimates of CL/F and AUC from NCA, because the comparison between patients and HVs would be confounded by other differences between the two study populations (e.g., HVs are often young males, and women or older people are commonly more affected by chronic inflammatory diseases and thus underrepresented in the HV studies). PopPK has the advantage to control for these factors when estimating the disease-related effect.

To accurately represent the confidence of the CL/F difference from the PopPK parameters, we simulated the CL/F of 1000 HVs and patients according to the reported statistical model and covariate parametrization using typical values and parameter uncertainty. The intervals shown in the forest plot are the 95% quantiles of the simulated distribution of CL/F differences. For drugs where no disease status covariate was included in the final model or where no PK difference was reported, we assumed that the difference in CL/F was deemed not clinically relevant. We represent this assumption in the forest plot by setting the confidence interval to the usual clinically not relevant limits of -20% and +25%. This allows to visualize also the drugs where no PK dfference between patients and HVs was found.

RESULTS

Drug (Sponsor)	Indication	Discussed PK difference (patients vs HV)	CL/F difference from PopPK	Metabolic pathways	Fraction excreted unchanged	Absolute oral bioavailability
Tofacitinib (Pfizer)	RA	-43% CL/F	-47.3%	CYP3A4 (major) CYP2C19	30% (urine)	74%
Upadacitinib (Abbvie)	RA	-25% CL/F	-24.6%	CYP3A4 (major) CYP2D6	38% (feces) 24% (urine)	NA
Baricitinib (Eli Lilly)	RA	NA	NA	CYP3A4	69% (urine) 15% (feces)	80%
Deucravacitinib (Bristol-Myers Squibb)	PsO / AD	-33% CL/F	-14.2%	CYP1A2 (major) CYP2B6/2D6, CES2, UGT1A9	26% (feces) 13% (urine)	99%
Tapinarof (Dermavant)	PsO	NA	NA	CYP, UGT, SULT	NA	NA
Apremilast (Celgene)	PsA	"1.4 times higher exposure"	-36.2%	CYP3A4 (major) CYP1A2/2A6 Hydrolysis	7% (feces) 3% (urine)	73%
Etrasimod (Pfizer)	UC	0%	-9.1%	CYP2C8/2C9/3A4/ 2C19/2J2, UGT, SULT	11% (feces)	NA
Ozanimod (Celgene)	UC MS	0%	-5.6% (UC) -13.4% (MS)	CYP3A4 (major) ALDH/ADH	Major excretion of metabolites	NA
Dalfampridine (Acorda)	MS	0%	NA	CYP2E1 (major) other CYP	90.3% (urine) <0.5% (feces)	NA
Fingolimod (Novartis)	MS	0%	NA	CYP4F2 (major) other CYP	<5% (feces)	93%
Teriflunomide (Sanofi-Aventis)	MS	0%	NA	Hydrolysis (major) Oxidation	37.5% (feces)	"complete bioavailability"
Dimethyl Fumarate (Biogen)	MS	0%	NA	TCA cycle	Trace amounts of MMF in urine	NA
Siponimod (Novartis)	MS	0%	NA	CYP2C9 (79.3%) CYP3A4 (18.5%)	Major fecal excretion of metabolites	84%
Ponesimod (Janssen)	MS	0%	NA	Non-CYP enzymes CYP2J2/3A4/3A5/4F3A/4 F12, UGT1A1/2B7	16% (feces)	84%
Abrocitinib (Pfizer)	AD	NA	-38.7%	CYP2C19 (53%) CYP2C9 (30%) CYP3A4 (11%) CYP2B6 (6%)	<1% (urine)	60%
Crisaborole (Anacor)	AD	NA	NA	Hydrolysis	Major renal excretion of metabolites	NA
Obeticholic Acid (Intercept)	BC	"moderately higher exposure"	NA	Glycine, Taurine conjugation	Minor excretion of obeticholic acid in feces	17%
Elafibranor (Ipsen)	BC	0%	NA	PTGR1 (major) CYP2J2, UGT	56.7% (feces) <0.1% (urine)	NA
Avacopan (ChemoCentryx)	ANCAV	-35% CL/F	-35.1%	CYP3A4	7% (feces) <0.1% (urine)	"highly bioavailable"

Abbreviations: HV=healthy volunteer; RA=rheumatoid arthritis; PsO=Psoriasis; PsA=psoriatic arthritis; AD=atopic dermatitis; UC=ulcerative colitis; MS=multiple sclerosis; BC=biliary cholangitis; ANCAV=antineutrophil cytoplasmic antibody-associated vasculitis; DMF=dimethyl fumarate; MMF=monomethyl fumarate; CYP=cytochrome P450; CES=carboxylesterase; UGT=uridine diphosphate glucuronosyltransferase; SULT=sulfotransferase; TCA=tricarboxylic acid; ALDH=aldehyde dehydrogenase; ADH=alcohol dehydrogenase; PTGR=prostaglandin reductase.



[1] Jover et al., 2002, The FASEB Journal: Down-regulation of human CYP3A4 by the inflammatory signal interleukin 6: molecular mechanism and transcription factors involved.
[2] Aitken et al., 2006, Annu. Rev. Pharmacol. Toxicol.: Regulation of drug-metabolizing enzymes and transporters in inflammation.
[3] Tian et al., 2024, CPT: Impact of chronic inflammatory diseases on clinical pharmacokinetics of antibody-based therapeutic proteins.
[4] U.S. Food and Drug Administration. Drugs@FDA database <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm> (2025).

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