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Inflammation is a major regulator of drug metabolizing enzymes and transporters: Consequences for the personalization of drug treatment

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ABSTRACT

Inflammation is an evolutionary process that allows survival against acute infection or injury. Inflammation is also a pathophysiological condition shared by numerous chronic diseases. In addition, inflammation modulates important drug-metabolizing enzymes and transporters (DMETs), thus contributing to intra- and interindividual variability of drug exposure. A better knowledge of the impact of inflammation on drug metabolism and its related clinical consequences would help to personalize drug treatment.

Here, we summarize the kinetics of inflammatory mediators and the underlying transcriptional and post-transcriptional mechanisms by which they contribute to the inhibition of important DMETs. We also present an updated overview of the effect of inflammation on the pharmacokinetic parameters of most of the drugs that are DMET substrates, for which therapeutic drug monitoring is recommended. Furthermore, we provide opinions on how to integrate the inflammatory status into pharmacogenetics, therapeutic drug monitoring, and population pharmacokinetic strategies to improve the personalization of drug treatment for each patient.

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Contents

1. Introduction	2
2. Roles of inflammation, kinetics, pivotal cytokines, and acute-phase proteins	2
3. Regulation of DMETs by inflammation	3
4. Pharmacological consequences of acute inflammation-induced metabolic phenoconversion in patients with acute inflammation	6
5. Pharmacological consequences of inflammation-induced metabolic phenoconversion in patients with chronic inflammation	14
6. How to integrate the inflammatory status in personalized medicine?	15

Abbreviations: ABC, ATP binding cassette; APP, acute phase protein; AUC, area under the curve; C/D, concentration/dose ratio; CKD, chronic kidney disease; Cmax, maximal concentration; Cmin, trough concentration; CAR, constitutive androstane/active receptor; CRP, C reactive protein; CYP, cytochrome P450; DAMP, damage-associated molecular pattern; DMET, drug metabolizing enzymes and transporters; FXR, farnesoid X receptor; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; MAPK, MAP kinases; MEGX, monoethylglycinexylidide; MPA, mycophenolic acid; NO, nitric oxide; PAMP, pathogen-associated molecular pattern; PPAR, peroxisome proliferator activation receptor; PXR, pregnane X receptor; RXR, retinoid X receptor- α ; SLC, solute carriers; TDM, therapeutic drug monitoring; TLR, toll like receptor; TNF- α , tumor necrosis factor α ; UDP-GT, UDP-glucuronyl transferase.

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7. Conclusion	17
Submission Declaration	17
Funding source	17
Acknowledgements	17
References	17

1. Introduction

The paradigm of personalized medicine aims to provide the right treatment at the right dose for each patient. A global knowledge of the patient, including his/her way of life, comorbidities, medications, and pharmacogenotypes, is required to propose such personalized pharmacological treatment.

Certain lifestyle, social, and environmental factors have been suggested to promote systemic chronic inflammation, which can, in turn, lead to disease, such as cardiovascular disease (Ketelhuth et al., 2019), chronic infectious disease and cancer (Deeks, Lewin, & Havlir, 2013), diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease, and autoimmune and neurodegenerative disorders (Furman et al., 2019). In addition, people face acute infections or injury episodes throughout their life that are resolved by intermittent increases in inflammation. Yet, several papers have suggested that inflammation can modulate drug-metabolizing enzyme and transporter (DMET) activity (Morgan, 2017; Shah & Smith, 2015). Therefore, a better knowledge of the impact of inflammation on DMETs and its related clinical consequences would help to understand inter and intraindividual variability of drug exposure and better manage drug exposure for each patient. Indeed, the clinical response to most drugs, *i.e.* efficacy or toxicity, is related to exposure to the drug or its active metabolites.

Several complementary pharmacological approaches have helped to ensure the most adapted drug exposure for each patient (Tucker, 2017), but few have addressed inflammation as a major source of drug pharmacokinetic variability.

Pharmacogenetics allows the identification of genetic variants, the presence of which can strictly contraindicate the use of a drug (HLA-B*5701 for abacavir) or contribute to explain interindividual pharmacokinetic or pharmacodynamic variability (Lauschke, Zhou, & Ingelman-Sundberg, 2019). Consequently, the determination of genotypes helps to predict a patient's phenotype and therefore to propose the right first dose of a drug when a treatment is initiated (Thervet et al., 2010). However, a study performed on 114 Hungarian liver donors reported that the CYP2C19 phenotype was well-predicted by genotypic data in only 40% of patients (Kiss, Vaskó, Déri, Tóth, & Monostory, 2018). These data suggest that the prediction of metabolic capacity based on the determination of pharmacogenetic polymorphisms may be blunted by other determinants, including co-medication that interferes with DMETs or any inflammatory comorbidities that may have occurred during the lifetime of an individual (Shah & Smith, 2015).

Therapeutic drug monitoring makes it possible to verify the total exposure to narrow therapeutic index drugs. It is a useful approach to ensure the longitudinal pharmacological follow-up of patients with chronic treatment (*i.e.*, immunosuppressants, antipsychotics, antifungals) and adapt the dose for each patient whenever intrinsic or external changes occur. Liver or kidney function or co-medication with drugs that affect DMETs are well-known variables that can affect drug exposure. However, the influence of inflammation has received less attention.

Finally, pharmacokinetic models are useful tools to predict inter-dose plasma exposure to escalate or de-escalate the dose of a drug (Petitcollin et al., 2019) during pharmacological follow-up. In addition to demographic information, these models consider classical features that contribute to inter- or intraindividual variability of drug exposure. However, the inflammatory status of the patient is rarely tested as a

covariate, except for pharmacokinetic modelling of the exposure of biologics used for the treatment of inflammatory diseases.

Here, we present the contribution of inflammation to the modulation of DMET activity and discuss its related clinical consequences, beyond pharmacogenetics and drug/drug interactions. Finally, on behalf of the French Society of Pharmacology and Therapeutics, we provide opinions on how to integrate inflammation to personalize pharmacological treatment.

2. Roles of inflammation, kinetics, pivotal cytokines, and acute-phase proteins

Inflammation is clinically defined as the presence of redness, swelling, and pain and results from a complex biological response to stimuli, such as pathogens, damaged cells, or irritants. It is a protective response, involving a wide range of host cells, blood vessels, proteins, and numerous mediators, aiming to eliminate the initial cause of cell injury, and necrotic cells to initiate the process of repair.

Inflammation can be classified as either acute or chronic. Acute inflammation, due to an infection for example, lasts a few days and is generally cleared by the immune system. Chronic inflammation is characterized by simultaneous destruction and healing of the tissue from the inflammatory process and the absence of any resolution of inflammation, giving rise to a host of diseases, such as cardiometabolic disease, autoimmune disease, or cancer (Netea et al., 2017).

Inflammation is induced when innate cells detect infection or tissue injury. The pattern-recognition receptors on immune cells sense “danger” from pathogen-associated molecular patterns (PAMPs) associated with pathogens or damage-associated molecular patterns (DAMPs) triggered by a wide range of host-derived endogenous stress signals. DAMPs are molecules, such as ATP, uric acid, and certain cytoplasmic and nuclear proteins that are released from damaged cells and contribute to sterile inflammation. Toll-like receptors (TLRs) are the major pattern-recognition receptors that are expressed on immune cells (monocytes, macrophages, neutrophils, and dendritic cells) and respond rapidly to the “danger” response. Bacterial and fungal nucleic acids are recognized by intracellular TLRs and other components by cell-surface TLRs. TLRs also recognize DAMPs (Kawai & Akira, 2010).

Activated immune cells initiate the inflammatory process and are considered to be the most important source of various proinflammatory mediators, such as cytokines, chemokines, leukotrienes, or prostaglandins, which regulate acute-phase protein (APP) production. These systemic changes are referred to as “acute-phase responses”, but they are produced under both acute and chronic inflammatory conditions.

Pro-inflammatory cytokines (mainly interleukin-1 β (IL-1 β), interleukin-6 (IL-6), tumor necrosis factor α (TNF- α)) and chemokines play a crucial role by recruiting additional immune cells to the site of infection for the phagocytosis and killing of pathogens. They can also activate nitric-oxide (NO) synthase 2 to produce NO in macrophages and hepatocytes (Nathan, 2002).

Elevated pro-inflammatory cytokines are required to initiate acute inflammation and maintain chronic inflammatory responses. Their biological activity occurs at very low concentrations through binding to specific high-affinity TLRs on the cell surface, leading to activation of the transcriptional factor NF- κ B (Tak & Firestein, 2001).

IL-1 β is a central mediator of innate immunity and inflammation. Its binding to functional TLRs induces the activation of NF- κ B and MAPK (MAP kinases) signaling pathways, which leads to the transcription of genes encoding most inflammatory cytokines (IL-6 and TNF- α), chemokines, cyclooxygenase-2, and the inducible NO synthase. IL-6 binds with high affinity to cells expressing both membrane IL-6R and gp130. Hepatocytes express membrane IL-6R and gp130 and the liver is considered to be the main target organ of IL-6. TNF- α is expressed as a transmembrane protein but can be cut to release its soluble form, with higher biological activity. Targets for TNF- α include two type transmembrane receptors, TNF receptor I (TNFR-I or CD120a) and TNF receptor II (TNFR-II or CD120b).

The acute-phase reaction is a complex, highly-conserved innate response to infection or tissue damage. It involves the above-mentioned signals and a set of plasma proteins, called APPs, which are mainly released from hepatocytes in response to IL-6. Thus, the acute-phase reaction is associated with increased C-reactive protein (CRP), orosomucoid, serum amyloid protein A, complement C3, haptoglobin, and fibrinogen release and reduced production of albumin, transferrin, and fibronectin. The levels of APPs in serum correlate with the degree of inflammation (Bauer, Press, & Trauner, 2013; Gabay & Kushner, 1999). For example, in cultured hepatocytes, IL-6 induces a marked increase of CRP and serum amyloid protein A mRNA levels (Dickmann et al., 2012). Circulating levels of cytokines and APP are useful biomarkers to detect inflammation and measure its intensity in clinical practice. Table 1 summarizes the kinetics of APPs.

As the acute inflammatory cascade develops to manage the “danger” signal, it is essential that controlled resolution begins, allowing immune homeostasis to return in an organized manner. At the peak of inflammation, anti-inflammatory cytokines, such as IL-10 and transforming growth factor-beta (Proto et al., 2018), as well as resolvins, lipoxins, and maresins initiate the resolution of inflammation.

3. Regulation of DMETs by inflammation

Preclinical models are useful tools to address the effect of infection-induced inflammation on drug metabolism in the absence of comorbidity. These models consist of injecting mice with lipopolysaccharide (LPS), a toxic component of Gram-negative bacterial cell walls, oral administration of enteropathogens, such as *Citrobacter rodentium* (Chaluvadi, Kinloch et al. 2009), or injection of parasites, such as *Schistosoma mansoni* (Mimche et al., 2014) or *Plasmodium chabaudi* (Mimche et al., 2019), to induce an inflammatory response. Indeed, these models all present an increase in proinflammatory cytokine transcription and release (see Table 2). Challenging primary culture hepatocytes with the major cytokines released during infection is another way to investigate the direct effect of inflammation on DMET expression and/or activity (Dickmann et al., 2012).

Other pre-clinical models mimic certain chronic inflammatory diseases, including colitis (Chaluvadi, Kinloch, et al., 2009; Masubuchi, Enoki, & Horie, 2008), arthritis (Ashino et al., 2007; Dickmann et al., 2012; Sanada, Sekimoto, Kamoshita, & Degawa, 2011), diabetes (Ghose et al., 2011; Wu & Lin, 2019; Yoshinari, Takagi, Sugatani, & Miwa, 2006), or extrahepatic cancer (Kacevska et al., 2013). Most studies have reported reduced expression of the main DMETs, notably members of the CYP 1A, 3A, 2B and 2C superfamilies, and, to a lesser extent, UDP-GT, as well as ATP-binding cassette (ABC) and solute carrier (SLC) transporters (Wu & Lin, 2019).

Overall, three major mechanisms have been proposed to explain the downregulation of inflammation on DMET expression and activity.

3.1. Inflammation induces transcriptional inhibition of many DMETs

Most studies using LPS as a trigger of inflammation have reported decreased mRNA and protein levels and reduced activity of certain hepatic CYPs commonly involved in drug metabolism, either at baseline

(see Table 2) or in response to challenge with pregnenolone-16 α -carbonile, an agonist of the pregnane X receptor (PXR) (Moriya, Kataoka, Fujino, Nishikawa, & Kugawa, 2012). For example, reduction of CYP3A11 mRNA levels was associated with decreased clearance of its substrates, nifedipine and testosterone (Moriya et al., 2012). CYP suppression occurred between 7 and 10 days post-oral inoculation of *Citrobacter rodentium* in mice (Chaluvadi, Kinloch, et al., 2009). Such kinetics of CYP down-regulation are consistent with a transcriptional inhibitory mechanism.

Similarly, mice infected with parasites (*Schistosoma mansoni* or *Plasmodium chabaudi*) (see Table 2) show CYP down-regulation. Again, reduced CYP and UDP-GT expression at the transcriptional and protein levels in infected mice are associated with increased exposure to nifedipine, caffeine, bupropion, tolbutamide, and midazolam (Mimche et al., 2019).

These findings all show that infection by bacteria or parasites may inhibit CYP transcription and expression, which translates into reduced CYP activity. The inhibition of liver microsomal CYP1A2 and CYP2B5 expression and activity occurs only at concentrations of LPS that promote an increase in the level of serum inflammatory cytokines and NO (De-Oliveira, Poça, Totino, & Paumgarten, 2015), suggesting that pro-inflammatory cytokines and NO may be intermediate molecular links between inflammation and CYP downregulation (Shah & Smith, 2015). Moreover, deletion of the gene encoding IL-6 prevented the down-regulation of CYP2D and CYP3A in *Clostridium rodentium*-infected mice, whereas the down-regulation of CYP4A remained unchanged (Nyagode, Lee, & Morgan, 2010). Furthermore, deletion of the gene encoding IFN- γ prevented the LPS-induced down-regulation of CYP2D, whereas it did not affect the inhibition of CYP3A and CYP4A in the same experimental model (Nyagode et al., 2010). These findings show heterogeneous effects of cytokines on CYP expression and activity, with differences in magnitude, potency (Dickmann, Patel, Rock, Wienkers, & Slatter, 2011), and time-course, depending on the administered infectious agent (see Table 2).

Similar downregulation of DMETs in preclinical models of certain chronic inflammatory diseases has been recently reviewed (Wu & Lin, 2019). Various models of colitis (Chaluvadi, Kinloch, et al., 2009; Masubuchi et al., 2008) and arthritis (Ashino et al., 2007; Dickmann et al., 2012; Sanada et al., 2011) show diminished hepatic expression and/or activity of many CYP450 enzymes (CYP3A, 4A, 2C, 1A2, and 2E1). Such down-regulation appears to correlate with an increase in pro-inflammatory cytokine concentrations (IL-6 and TNF- α , as well as IFN- γ , IL-2, IL-1 α , and IL-1 β) (Chaluvadi, Kinloch, et al., 2009; Masubuchi et al., 2008; Sanada et al., 2011) and could explain the increased concentrations of propranolol (Guirguis & Jamali, 2003) and verapamil (Ling & Jamali, 2005) observed in adjuvant-induced arthritis.

IL-6 is one of the most abundant cytokines released in the plasma of infected mice (Chaluvadi, Kinloch, et al., 2009). IL-6 represses CYP3A4 expression (Yang et al., 2010) and decreases CYP3A-dependent clearance in a dose-dependent manner in human hepatocyte cells in culture (Dickmann et al., 2011). Moreover, pretreatment of human hepatocytes with an IL-6 monoclonal antibody inhibited the decrease in IL-6-induced CYP3A clearance (Dickmann et al., 2011), providing definitive proof for the contribution of IL-6 in reducing CYP3A-dependent clearance. However, the inhibitory effect of IL-6 is not limited to CYP3A, as a large panel of CYPs was also shown to be down-regulated in murine models of infection (Table 2), a genetic murine model of arthritis (Ashino et al., 2007), and cultured hepatocytes (Aitken & Morgan, 2007).

Similar experiments have also suggested a major role of TNF- α in CYP downregulation, as deletion of the gene encoding the TNF- α receptor (Kinloch, Lee, van Rooijen, & Morgan, 2011) or treatment with a biologic drug that neutralizes soluble TNF- α (Nyagode, Jahangardi, Merrell, Tansey, & Morgan, 2014) prevented the downregulation of CYP3A11 and CYP3A25 in *Citrobacter rodentium*-infected mice. Infliximab treatment of pre-adjuvant arthritic rats resulted in

Table 1
Upregulated acute-phase proteins used as inflammatory biomarkers.

Acute phase protein	Main role	Normal range	Time after inflammatory stimulus (in hours)	Maximum fold change in plasma concentration
CRP (C-reactive protein)	Binding to pathogens and damaged cells, opsonin, complement activation	<0.5 mg/L	6–12 h	x 1000
PCT (procalcitonin)	Unknown	<10 pg/mL	6– 8 h	x 400–1000
SAA (Serum amyloid A)	Opsonin, regulation of innate defense, induction of extracellular matrix degrading enzymes, chemoattractant, apolipoprotein with HDL, regulation of lipid metabolism	<10 mg/L	6–12 h	x 1000
α 1-glycoprotein (or orosomucoid)	Binding of plasma proteins and mediators, chaperone, regulation of innate defense	<1.5 g/L	12 h	x 2–4
Haptoglobin	Scavenging of hemoglobin, antioxidants, angiogenesis, chaperone	0.5–2 g/L	12 h	x 2–4
Fibrinogen	Clot formation	2–4 g/L	12 h	x 2–4
AAT (α 1-anti trypsin)	Enzyme inhibition	2–4 g/L	12 h	x 2–4
C3 complement	Pathogen recognition, destruction, chemotaxis, opsonin, vasoregulation	0.8 à 18 g/L	48 h	x 1.5
Ceruloplasmin	Iron and copper homeostasis	0.2–0.6 g/L	48 h	x 1.5

significantly higher total CYP protein content than that in untreated pre-adjuvant arthritic rats (Ling & Jamali, 2009). These data, along with those from *in vitro* hepatocyte experiments showing that TNF- α powerfully regulates CYP levels (Kinloch et al., 2011; Nyagode et al., 2010), provide strong evidence for the role of TNF- α in CYP downregulation.

Conversely, several studies reported induction of certain CYPs: CYP2D9 in rodents models of infectious colitis (Chaluvadi, Kinloch, et al., 2009; Chaluvadi, Nyagode, Kinloch, & Morgan, 2009) or diabetes (Gwak, Yoo, & Kim, 2020) (see Table 2), CYP3A13 in mice with collagen antibody-induced arthritis (Dickmann et al., 2012) or oral infection by *Citrobacter rodentium* (Richardson et al., 2006), CYP4A and CYP2E sub-families in LPS-treated F344 rats (Morgan, 1997). Experimental studies performed in various rodent models of diabetes (Wu & Lin, 2019) have also provided conflicting results in terms of expression of DMETs, with expression and activity either increased (Yoshinari et al., 2006) or decreased (Ghose et al., 2011). All these discordant results could be related to the differences in rodent species (rat vs mice) and strains (Sprague-Dawley rats vs Zucker diabetic fatty rat for example), and inflammatory stimuli that were used (injection of LPS, chemical irritant or infectious agent) in different experimental conditions (see Table 2 and the review of Morgan et al (Morgan, 1997)).

The effect of inflammation on other enzymes involved in drug metabolism and on transporters has received less attention. Infection by *Citrobacter rodentium* (Kinloch et al., 2011) or *Plasmodium chabaudi* (Mimche et al., 2019) significantly reduces hepatic flavin monooxygenase mRNA levels. Infection by *Plasmodium chabaudi* (Mimche et al., 2019) or *Clostridium rodentium* or treatment with LPS (Richardson, Sherman, Kalman, & Morgan, 2006) significantly down-regulated several genes encoding the hepatic UDP-GT1A1, 1A9, and several of those of the UGT2B subfamily, an effect associated with the reduced expression of UDP-GT1A1 and UDP-GT2B protein. Again, the effect of inflammation on UDP-GT regulation appears to be cytokine-dependent and UDP-GT isoform specific, as also reported for CYP. However, IL-6 downregulates most phase 2 enzymes involved in drug metabolism in human primary hepatocytes (Keller et al., 2016).

An *in vitro* study on human liver microsomes suggested that certain nonsteroidal anti-inflammatory drugs may have an inhibitory potential on UDP-GT isoforms, suggesting that certain mediators of the cyclooxygenase-dependent pathway may be involved in the regulation of DMET activity. However, the underlying mechanism and the clinical relevance in terms of UDP-GT substrate clearance need to be further investigated (Joo et al., 2015).

The hepatic transporters involved in drug clearance belong to two gene families, ATP-binding cassette (ABC) and SLC. Significant down-regulation of hepatic mRNA levels of SLC22a4, SLC0a4, and SLC02b1, as well of ABCb1, ABCg2, has been reported in *Citrobacter rodentium*-infected mice relative to controls (Merrell, Nyagode, Clarke, Cherrington, & Morgan, 2014). This effect was blocked in infected

mice lacking IL-6 or TNF α (Merrell et al., 2014), again suggesting a key role of these cytokines in the downregulation of certain SCL and ABC transporters. A study on primary human hepatocytes challenged with IL-6 has extended these findings to numerous transporters of the ABC and SLC families (Keller et al., 2016).

The binding of pro-inflammatory cytokines to their specific receptors leads to the activation of several transcription factors, including NF- κ B. The direct binding of NF- κ B to DMET promoter regions inhibits the heterodimerization of nuclear retinoid x receptor (RXR)- α to constitutive androstane/active receptor (CAR), pregnane X receptor (PXR), and peroxisome proliferator activation receptor (PPAR) nuclear receptors. Yet, the heterodimerization of RXR to other nuclear receptors plays a central role in the regulation of genes encoding DMETs (Keller et al., 2016; Wu & Lin, 2019). Moreover, inflammation related to *Plasmodium chabaudi* is associated with the downregulation of CAR and farnesoid X receptor (FXR) and, to a lesser extent, PXR and RXR mRNA (Mimche et al., 2019). Thus, within the complex network that links transcriptional factors with the expression of DMET, NF- κ B pathway activation by pro-inflammatory cytokines contributes to the inhibition of DMET transcription observed during inflammation (Keller et al., 2016).

3.2. Inflammation induces NO-dependent proteasome degradation of DMETs

Several studies have suggested that post-transcriptional mechanisms may also modulate CYP activity. A chronic allergic murine model induced by repeated administration of ovalbumin showed down-regulation of CYP 1A2, CYP2C, 2E1, and CYP3A activity, although CYP protein expression remained unchanged relative to that of control animals (Tanino et al., 2019). IL-1 β challenge in cultured rat hepatocytes decreased CYP3A1 protein expression by 40% and reduced its activity within 6 h (Lee, Pohl, & Morgan, 2009). Such rapid kinetics suggest that post-transcriptional mechanisms may be involved in the early downregulation of CYP3A1. Several studies have reported that early cytokine-mediated downregulation of CYP is inhibited by a NO synthase inhibitor (Carlson & Billings, 1996) or proteasome inhibitor (Lee et al., 2009; Morgan, 2017). Similarly, effective inhibition of NO synthase reduced the hydrolase activity of several CYP enzymes but did not impair the downregulation of CYP2C29 or CYP3A11 mRNA expression or CYP2C, CYP2E, or CYP34 protein expression in rats treated with LPS (Sewer, Barclay, & Morgan, 1998). Finally, native CYP2B6 protein was rapidly downregulated in HeLa cells within 3 h of treatment with a NO donor, whereas the level of its mRNA was not (Lee et al., 2017). These data all suggest that NO and proteasome-dependent pathways are likely to be involved in the early phase of CYP protein down-regulation. Activation of the inducible NO synthase (Mimche et al., 2019) promoted by IL-1 β , IFN- γ , and TNF- α during the inflammatory response leads to increased NO synthesis and release, which in turn

Table 2Released cytokines and changes in liver mRNA/protein expression and activity of main cytochromes (CYP1A, 3A, 2B, 2C and 2D) and UGT1A in several experimental animal models of infection and chronic inflammation^a.

Inflammatory stimulus	Animal species	Released cytokines	CYP	1A	3A	2B	2C9 ^b	2C19 ^b	2D	UGT1A	References
Lipopolysaccharide	129S1/svImJ mice	IL-1 β , IL-6, TNF- α	mRNA Protein Activity	Decreased - -	Decreased Decreased -	Decreased Decreased -	Decreased Unchanged -	- -	- -	Decreased Decreased -	(Richardson & Morgan, 2005; Richardson, Sherman et al, 2006)
Lipopolysaccharide (>5 mg/kg bw)	DBA-2 mice	TNF- α , IL-1 β , IFN γ , IL-6, IL-17, IL-2, IL-10, IL-4	mRNA Protein Activity	- - Decreased	- - -	- - Decreased	- - -	- -	- -	- -	(De-Oliveira et al., 2015; Moriya et al., 2012)
<i>Citrobacter rodentium</i>	C3H/HeOJ mice	IL-1 β , IL-6, TNF- α	mRNA Protein Activity	Unchanged - -	Decreased - Decreased	- -	Decreased Decreased -	- -	- -	Decreased Decreased -	(Richardson, Sherman et al, 2006; Richardson, Sherman, Kalman, & Morgan, 2006)
<i>Citrobacter rodentium</i>	C57BL/6 mice	IL-6, TNF- α , IL-1 β	mRNA Protein Activity	Decreased - -	Decreased Unchanged -	Unchanged Decreased -	Unchanged Decreased -	- -	Increased Decreased -	- -	(Kinloch et al., 2011)
<i>Citrobacter rodentium</i>	C57BL/6 mice	TNF- α , IL-6, IFN- γ , IL-10, IL-1 β	mRNA Protein Activity	Increased - -	Decreased Unchanged -	Decreased - -	Unchanged - -	- -	Unchanged -	- -	(Nyagode et al., 2014)
<i>Citrobacter rodentium</i>	C57BL/6 mice	IL-2, IL-6, IL-13, IFN β , MCP-1, increased IL-1 β , IL-4, IL-5, IL-9, IL-10 unaffected	mRNA Protein Activity	Decreased - -	Decreased Decreased -	Decreased Decreased -	Decreased Decreased -	- -	Increased Increased -	- -	(Chaluvadi, Kinloch, et al., 2009)
<i>Schistosoma mansoni</i> (45 days post infection)	Swiss Webster mice	IL-4, IL-5, IL-13, IL-10, TGF β 1, TGF β 2, IL-1 β , IL-6, IFN γ , TNF- α	mRNA Protein Activity	Decreased Decreased -	Decreased Decreased -	Decreased Decreased -	Decreased Decreased -	Decreased Decreased -	Decreased Decreased -	Decreased -	(Mimche et al., 2014)
<i>Plasmodium chabaudi chabaudi</i>	C57BL/6 mice	IL-1 β , TNF- α , IFN γ , IL-6 (mRNA)	mRNA Protein Activity	Decreased - Decreased	Decreased Decreased Decreased	- -	Decreased Decreased Decreased	Decreased Decreased Decreased	Unchanged Decreased Decreased	Decreased -	(Mimche et al., 2019)
Ovalbumin - multiple challenges	ICR mice	-	mRNA Protein Activity	Unchanged Unchanged Decreased	Unchanged Unchanged Decreased	- -	Unchanged Unchanged Decreased	- -	Unchanged Unchanged Decreased	- -	(Tanino et al., 2019)
Human T-cell leukemia virus type I transgenic mice (rheumatoid arthritis model)	BALB/c mice	IL-1 β , IL-6, TNF- α unaffected	mRNA Protein Activity	- - -	Decreased Decreased Decreased	- -	Unchanged -	- -	- -	- -	(Ashino et al., 2007)
Collagen antibody induced arthritis	BALB/c mice	IL-1 β , IL-6, SAA, IL-2, TNF- α unaffected	mRNA Protein Activity	Decreased - Decreased	Decreased -	Decreased -	Decreased -	- -	+/- Unchanged	Decreased -	(Dickmann et al., 2012)
<i>Mycobacterium tuberculosis</i> (adjuvant arthritis model)	Lewis rats	TNF- α , IL-1 β , IL-1 α , IL-6	mRNA Protein Activity	- -	Decreased Decreased Decreased	Decreased Decreased Decreased	- -	- -	- -	- -	(Sanada et al., 2011)
Trinitrobenzene sulfonic acid-induced colitis (model of inflammatory bowel disease)	Wistar rats	IL-6	mRNA Protein Activity	- Unchanged Decreased	Decreased Decreased	- -	- -	Decreased Decreased	- -	- -	(Masubuchi et al., 2008)
<i>Citrobacter Rodentium</i> (model of inflammatory bowel disease)	C57BL/6 mice	IL-2, IL-6, TNF- α , KC, IFN γ , MIP1 α , MCP-1, RANTES	mRNA Protein Activity	Decreased Decreased -	Decreased Decreased -	Decreased Decreased -	Decreased Decreased -	- -	Increased Increased -	- -	(Chaluvadi, Nyagode, et al., 2009)
<i>Mycobacterium butyricum</i> (adjuvant arthritis model)	Sprague-Dawley rats	TNF- α	mRNA Protein Activity	- Decreased Decreased	- Decreased Decreased	- -	- -	- -	- -	- -	(Ling & Jamali, 2005)
diabetes	Zucker fatty rat	-	mRNA Protein Activity	Unchanged Unchanged Unchanged	Decreased Decreased Decreased	Decreased Decreased Decreased	Unchanged Unchanged Unchanged	Decreased Decreased Decreased	- -	- -	(Yao et al., 2019)
Streptozotocin-induced diabetes mellitus	Sprague-Dawley rats	-	mRNA Protein Activity	- Increased -	- Increased -	- Increased -	- -	- Decreased -	- Increased -	- -	(Gwak et al., 2020)
Engelbreth-Holm-Swarm sarcoma (model of	C57BL/6 mice	IL-6	mRNA Protein	- -	Decreased -	- -	- -	- -	- -	- -	(Kacevska et al., 2013)

(continued on next page)

Table 2 (continued)

Inflammatory stimulus	Animal species	Released cytokines	CYP	1A	3A	2B	2C9 ^b	2C19 ^b	2D	UGT1A	References
extra-hepatic cancer)			Activity		Decreased						
High fat diet	Sprague-Dawley rats	-	mRNA	Decreased	+/-	Decreased	-	Decreased	Unchanged	Decreased	(Zhang et al., 2019)
			Protein	Decreased	+/-	-		Decreased	-	-	
			Activity	Decreased	Unchanged	Decreased		Decreased	Unchanged	Decreased	

IFN β : beta interferon, IFN γ : gamma interferon, IL: interleukin, MIP-1 α : macrophage inflammatory protein 1 α , MCP-1: monocyte chemoattractant protein-1, KC: chemokine CXCL1, mRNA: messenger ribonucleic acid, RANTES: chemokine CCL5, SAA, serum amyloid A, TNF α : tumor necrosis factor alpha, -: not determined, +/- according to the considered isoenzymes.

^a List of publications indicated in this table is not exhaustive. For example, because studies investigating the impact of diabetes on various animal models were recently reviewed (Wu & Lin, 2019), this table does not include the works discussed in that review, except those which were published after its publication.

^b According to Yao et al. (2019), human CYP2C9 and CYP2C19 corresponds to CYP2C11 and CYP2C22 in rats.

reduces CYP activity through reversible binding to the heme moiety or tyrosine and cysteine S-nitrosilation or nitration. In addition, NO induces proteasome-dependent CYP3A4 inhibition, as a proteasome inhibitor blocks IL-1 β and NO-induced downregulation of CYP3A4 (Lee et al., 2009). Given that IL-1 β is a cytokine synthesized during the initial phase of the inflammatory response, these data all suggest that the functional inhibition of CYP activity occurs early in the inflammatory process.

3.3. Inflammation induces epigenetic modifications of DMET genes

Epigenetic changes regulate the expression and activity of genes involved in DMETs, as recently reviewed (Lauschke et al., 2019), and contribute to interindividual differences in drug responses (Ivanov, Barragan, & Ingelman-Sundberg, 2014). The level of DNA methylation in the promoters of several CYPs (CYP3A4, CYP1A2, CYP2C19 and UDP-GT1A4) inversely correlates with their levels of expression in adult liver (Habano et al., 2015). Similarly, the modification of histone patterns inversely correlates with the level of expression of several drug transporters (ABCb1, ABCg2) in prostate carcinoma (Henrique et al., 2013). Consequences on DMET expression or activity are expected, as inflammation itself also induces epigenetic regulation of the innate immune response (Zhang & Cao, 2019) and triggers the release of certain miRNAs from immune cells (Kugler, Klein, & Zanger, 2020). Indeed, methylation levels at the CYP11A1 locus significantly correlate with CRP levels in the serum of patients with bipolar mania, suggesting an association between inflammation and epigenetic changes of CYP (Sabuncian, Maher, Bahn, Dickerson, & Yolken, 2015). Furthermore, miRNAs have been reported to contribute to the variability of CYP, including reduced expression and activity of CYP2C9, CYP2C8, CYP2C19 (Rieger, Reutter, Hofmann, Schwab, & Zanger, 2015), CYP2D6 (Zeng et al., 2017) and CYP3A4 (Kugler et al., 2020). A recent study evidenced upregulation of several miRNAs in livers from donors with elevated CRP concentrations compared to those with a normal concentration (Kugler et al., 2020). Some of these miRNAs were able to attenuate DMET expression and activities or to target nuclear receptors to block gene transcription, CYP2C19 and CYP3A4 being the top downregulated.

In summary (see Fig. 1), these data all suggest that acute or chronic inflammation can inhibit the level and activity of major CYPs and, to a lesser extent, type 2 enzymes and ABC and SLC transporters involved in drug pharmacokinetics. These inhibitory effects may occur both in the intestine (Simon et al., 2019) and liver, leading to impaired absorption and pre-systemic and hepatic metabolic phenoconversion. In acute inflammation, phenoconversion would result in a shift towards poorer metabolizing phenotype, providing there are no other cause of inhibition. In chronic inflammation, treatment with a drug that inhibits the inflammatory pathway (i.e. IL-6 monoclonal antibody) might revert the phenotype to its physiological status, providing there is no other cause

of induction. Thus, inflammation can contribute to the intra and inter-individual variability of drug responses.

4. Pharmacological consequences of acute inflammation-induced metabolic phenoconversion in patients with acute inflammation

Approximately 80% of all drugs are primarily metabolized by CYP isoforms, notably CYP1A2, 2D6, 3A4, 2C9, and 2C19. As a consequence, inflammation could theoretically influence their pharmacokinetics. This point is of high clinical relevance for drugs with a narrow therapeutic index, which are candidates for TDM. Table 3 presents the effect of inflammation on the blood or plasma exposure and/or pharmacokinetic parameters of the main drugs for which TDM is routinely performed.

4.1. Psychotropic drugs (see Table 3)

Numerous studies have highlighted the impact of inflammation on clozapine metabolism. Several case reports have described elevated concentrations of clozapine in patients experiencing acute inflammatory episodes associated with clinical signs of intoxication (de Leon & Diaz, 2003; Haack et al., 2003; Jecel et al., 2005). However, an increase in the clozapine and norclozapine trough concentration (C_{min}) and clozapine concentration/dose ratio (C/D) was observed in two patients, without symptoms of intoxication (Ruan et al., 2018). This link between the inflammatory status and clozapine pharmacokinetics was later confirmed by retrospective comparative studies using CRP levels as a marker of inflammation. Several studies on retrospective TDM data have reported an impact of abnormal CRP values on the clozapine concentration and C/D and a decrease in the metabolic clozapine/norclozapine ratio (Hefner, Shams, 2016; Pfuhlmann et al., 2009). Unfortunately, safety data were not available in these studies.

Little data are available for other antipsychotic drugs. An impact of inflammation on the pharmacokinetics of risperidone was described in two clinical cases (Hefner et al., 2015a) and confirmed in a retrospective comparative study. An increase in the C/D of the risperidone active moiety has been observed in patients with CRP > 5 mg/L (Hefner et al., 2016). However, the impact on the pharmacokinetics appears to be lower for risperidone than clozapine (increase in the C/D of 24.2 vs 48.0%). Although safety data were also lacking for risperidone, the clinical impact should be minimal. By contrast, no impact of the CRP value was observed on the pharmacokinetics of quetiapine in the same study. Concerning antidepressant drugs, one retrospective comparative study showed that the CRP concentration was not associated with the pharmacokinetics of citalopram or venlafaxine (Hefner, Shams, 2015; Hiemke et al., 2018). These results confirm a different impact of inflammation on psychotropic drug metabolism depending on the CYP isoform and their respective contribution in the drug clearance. Given that other psychotropic drugs are highly metabolized, an impact of

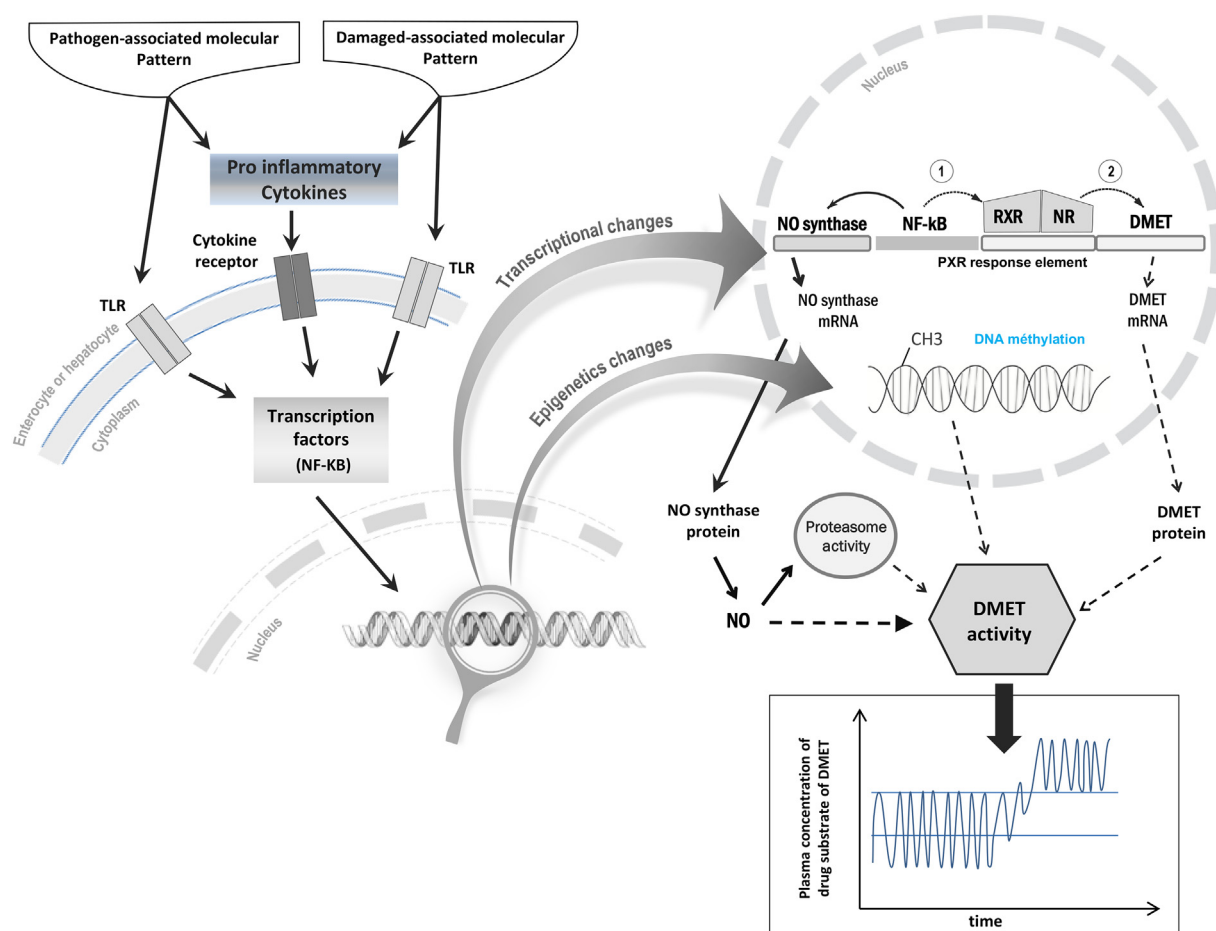


Fig. 1. Scheme of the inhibitory influence of inflammation on drug-metabolizing enzyme and transporter (DMET) activity, leading to overexposure to drugs that are DMET substrates and have a narrow therapeutic index. Pathogen-associated molecular patterns or damage-associated molecular patterns stimulate pro-inflammatory cytokine pathways, leading to transcriptional and post-transcriptional changes in DMETs. Transcriptional mechanisms involve NF- κ B activation, which inhibits the heterodimerization of nuclear retinoid x receptor (RXR)- α to other constitutive nuclear receptors (NR) (1), thus inhibiting DMET transcription (2) (under the magnifying glass). Non transcriptional mechanisms involve the direct inhibition of DMET by NO and the induction of proteasome-dependent CYP3A4 inhibition by NO. Finally, epigenetic changes, such as DNA methylation in response to inflammation, contribute to reduced DMET activity (under the magnifying glass). NR: nuclear receptor, including the peroxisome proliferator activating receptor, pregnane X receptor, retinoid x receptor- α , and constitutive androstane receptor. Solid lines indicate activation and dotted lines indicate inhibition.

inflammation would be expected for many. However, only scant data are available to support this hypothesis and further studies are needed, including comparative clinical trials.

4.2. Other central nervous system drugs (see Table 3)

There is only limited information on the impact of inflammation on the pharmacokinetics of antiepileptics and sedative drugs.

In a recent retrospective comparative study, an increase of the C/D of perampanel was observed in epileptic patients with CRP >15 mg/L (Yamamoto et al., 2018). In a case report on an eight-year-old girl, for whom clobazam (also mainly metabolized by CYP3A4) was co-administered, no impact on the clobazam C/D ratio was observed (Yamamoto et al., 2018). By contrast, an increase in the metabolism and plasma clearance of valproic acid and phenytoin has been observed in traumatic brain injury patients (Anderson, Temkin, Awan, Winn, & Winn, 2007; McKindley et al., 1997). The authors hypothesized that increased clearance of these drugs could be explained by changes in both pro- and anti-inflammatory factors in this population.

The impact of inflammation on the pharmacokinetics of midazolam was studied using population pharmacokinetics models on critically ill adult and pediatric populations. A first model was developed based on 26 critically ill Dutch children for whom a decrease in the clearance of midazolam correlated with disease severity but not CRP levels or

leucocyte counts (Vet, de Hoog, Tibboel, & de Wildt, 2012). In 2016, a model developed on a larger cohort (83 patients and 523 concentration data points) demonstrated that midazolam clearance was associated with CRP concentration and organ failure but not with IL-6 or

TNF- α concentrations (Vet et al., 2016). The impact of inflammation on the pharmacokinetics of midazolam has also been observed in other populations (full-term neonates and critically ill and healthy adult populations) but not in preterm neonates (Brussee et al., 2018; Franken et al., 2018). These heterogeneous results highlight the multifactorial aspect of the pharmacokinetic variability of critically ill patients, inflammation likely being one among many factors. Further studies are required, including safety data, to better describe the influence of inflammation on antiepileptic and sedative drug metabolism.

4.3. Immunosuppressive drugs (see Table 3)

In a study of 13 kidney transplant patients with a urinary tract infection, the concentrations of tacrolimus were higher during treatment with ertapenem than those measured before the infection. Although no biomarkers of inflammation were presented in this study, it can be hypothesized that the increased exposure to tacrolimus may have been related to the episode of acute infection that required antibiotic treatment (Bora et al., 2012). Consistent with this hypothesis, the C_{min} , AUC 0–4 h, T_{max} , and C_{max} of tacrolimus were reported to be

Table 3

Studies evaluating the impact of acute inflammatory episodes on the pharmacokinetics of drugs that are candidates for therapeutic drug monitoring

Pharmacological class and drug	Mains enzyme (transporter) involved	Study type	Patients number (plasma/blood samples)	Population study (country)	Duration of the phenoconversion	Concentration of inflammatory biomarkers	Pharmacokinetic consequences	Clinical consequences	References
Antipsychotics clozapine	CYP1A2	prospective observational study	14 (70)	Schizophrenic patients with influenza vaccination (Finland)	na	No difference in CRP after vaccination	No difference in [clozapine] and [metabolites] after vaccination.	na	(Raaska, Raitasuo, & Neuvonen, 2001)
clozapine	CYP1A2	retrospective comparative study	63 (63) (36 with therapeutic [clozapine]* and 27 with [clozapine] > 800 ng/mL)	Heterogeneous psychiatric patients (Germany)	na	CRP: 0.69 ± 1.42 mg/L (therapeutic [clozapine]); 3.64 ± 6.13 mg/L ([clozapine] > 800 ng/mL)	Higher frequencies of increased CRP (> 5 mg/L) in patient with elevated [clozapine]	na	(Pfuhlmann et al., 2009)
clozapine	CYP1A2	retrospective comparative study	33 (116): CRP ≥ 5 mg/L	Heterogeneous psychiatric patients (Germany)	na	CRP: 19.0 [range: 5.1-242.0] (≥ 5 mg/L group); 3.5 [range: 0.5-4.7] mg/L (< 5 mg/L group)	Increased C/D and decreased norclozapine/clozapine metabolic ratio in patients with CRP ≥ 5 mg/L	na	(Hefner et al., 2016)
clozapine	CYP1A2	retrospective observational study	16 corresponding to 18 episodes of inflammation /infection (46)	Schizophrenic patients with inflammation /infection (China)	na	na	Increased C/D in 16/18 episodes. Reducing the clozapine dose to the half would be advisable in 11 episodes and to one-third in 5 episodes.	na	(Ruan, Zang, Cheng, Wang, & de Leon, 2020)
clozapine	CYP1A2	case report	2	Schizoaffective disorder patient with dermatitis and pulmonary infection (China)	about 4-5 days	na	Increased C/D, [clozapine] and [norclozapine] during infection	na	(Ruan et al., 2018)
clozapine	CYP1A2	case report	4	Psychiatric patients (Netherlands)	na	CRP: 116 mg/L na na na na	[clozapine]* (dose): 1012 ng/ml (600 mg) 1824 ng/mL (400 mg) 2349 ng/mL (500 mg) 915 ng/mL (500 mg)	Clinical deterioration, loss of appetite, vomiting, somnolence	(Haack et al., 2003)
clozapine	CYP1A2	case report	1	Adult schizophrenic with severe respiratory infection (USA)	na	na	[clozapine]* (dose): 1245 ng/mL (600 mg)	Sedation and problems walking	(de Leon & Diaz, 2003)
clozapine	CYP1A2	case report	1	Adult with maniac and paranoid syndrome and urinary infection (Germany)	na	CRP at day 13: 81.5 mg/L	[clozapine]* (dose) at day 17: 1006 ng/mL (200 mg)	na	(Jecel et al., 2005)
clozapine	CYP1A2	case report	1	Adult with schizophrenia, Crohn disease and admitted for a suspected gastrointestinal infection	na	CRP at admission: 130 mg/L	[clozapine]* (dose) - 1 month before admission: 627.1 ng/mL (900 mg) - At admission: 2965.4 ng/ml (900mg)	na	(Espnes, Heimdal, & Spigset, 2012)
risperidone	CYP2D6	case report	2	Adult psychiatric patients (Germany)	about 2 days	CRP range: 0.8 to 110.0 mg/L	Simultaneous evolution of CRP and C/D during the follow-up of 16 and 5 days	na	(Hefner, Falter et al 2015)
risperidone	CYP2D6	retrospective comparative study	32 (102): CRP > 5 mg/L	Heterogeneous psychiatric patients (Germany)	na	CRP: 11.0 [range: 5.6-110.0] (> 5 mg/L group); 2.7 [range: 0.0-4.8] mg/L (< 5 mg/L group)	Increased risperidone +OH-risperidone C/D in patients with CRP ≥ 5 mg/L No difference in risperidone/OH-risperidone metabolic ratio between 2 groups	na	(Hefner et al., 2016)

risperidone	CYP2D6	case report	1	56-year-old men with schizophrenia and atypical pneumonia	na	CRP : 30.0 mg/L	Increased risperidone + OH-risperidone concentration to 405 nmol/L 1 week after admission (therapeutic range 50-140 nmol/L).	no adverse effect was observed	(Helland et al., 2018)
quetiapine	CYP3A4	retrospective comparative study	40 (101): CRP > 5 mg/L	Heterogeneous Psychiatric patients (Germany)	na	CRP: 1.5 [range : 5.3-116.0] (> 5 mg/L group); 2.8 [range : 0.2-4.5] mg/L (< 5 mg/L group)	No difference in norquetiapine/quetiapine metabolic ratio or quetiapine C/D between the 2 groups	na	(Hefner et al., 2016)
Antidepressants citalopram	CYP2C19	retrospective comparative study	30 (30) (15 with CRP > 5 mg/L and 15 with CRP < 5mg/L)	Heterogeneous psychiatric patients (Germany)	na	CRP: 13 [range :5.2-37.0] (> 5 mg/L group); 2.0 [range :0.5-4.7] mg/L (< 5 mg/L group)	No difference in C/D and metabolic ratio between the 2 groups	na	(Hefner, Shams, et al., 2015)
venlafaxine	CYP2C19 CYP2D6	retrospective comparative study	78 (78) (39 with CRP > 5 mg/L and 39 with CRP < 5mg/L)	Heterogeneous psychiatric patients (Germany)	na	In CRP: 11 [range: 5.3-232.0] (> 5 mg/L group); 3.2 [range: 0.0-4.8 mg/L] mg/L (< 5 mg/L)	No difference in C/D and metabolic ratio between the 2 groups	na	(Hefner et al., 2016)
Antiepileptics perampanel	CYP3A4	retrospective comparative study	111 (111) (23 with CRP > 15 mg/L and 88 with CRP <15mg/L)	Heterogeneous epileptic patients (Japan)	C/D ratio returned to baseline within 1 week after normalization of CRP (case presentation of one pediatric patient)	In CRP > 15 mg/L group: 42 mg/L [range : 15-102 mg/L]	Increased C/D ratio in patients with CRP > 15 mg/L both in the presence and absence of comedication with enzyme-inducing antiepileptics	No adverse events were recorded	(Yamamoto et al., 2018)
clobazam	CYP3A4	case report	1	Child with Rett syndrome and pneumonia (Japan)	na	na	No change in [clobazam] or [N-desmethyclobazam] during the study period of 77 days	No adverse events were observed	(Yamamoto et al., 2018)
Sedative drugs midazolam	CYP3A4	external evaluation of a previously developed PK model (Vet et al., 2016)	136 (1045)	Neonates, infants, children and adults (Netherlands)	na	CRP: 0.1 to 341 mg/L	MPE <30% for predicted CL in postoperative or critically ill patients and term neonates, critically ill and healthy adults. MPE > 180% in preterm neonates	na	(Brussee et al., 2018)
midazolam	CYP3A4	prospective observational study (PK analysis)	83 (523)	Critically ill children (Netherlands)	na	In simulations, CRP of 300 mg/L was associated with 65% lower clearance compared to 10 mg/L CRP: 92 [range: 1-625] mg/L	Association between CL and: - CRP - organ failure No association between CL and IL-6 and TNF α levels	na	(Vet et al., 2016)
midazolam	CYP3A4	prospective observational study (PK analysis)	45 (192)	Terminally ill adult patients (Netherlands, 91.1% Caucasian)	na	CRP: 92 [range: 1-625] mg/L	Correlation between CL and albumin or CRP (depending on the order on the backwards elimination in covariates selection)	na	(Franken et al., 2017)
midazolam	CYP3A4	prospective observational study (PK analysis)	21 (na)	Critically ill children (Netherlands)	na	na	No association between CL and inflammatory markers (CRP and leucocytes count). Correlation between CL and disease severity	na	(Vet et al., 2012)
Immunosuppressant drugs (mTOR inhibitor) sirolimus	CYP3A4/5 (Pgp)	prospective observational study (PK analysis)	52 (676)	Children with vascular anomalies (USA)	na	na	Drop of about 50% of CL during documented infection	na	(Mizuno et al., 2017)

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Table 3 (continued)

Pharmacological class and drug	Mains enzyme (transporter) involved	Study type	Patients number (plasma/blood samples)	Population study (country)	Duration of the phenoconversion	Concentration of inflammatory biomarkers	Pharmacokinetic consequences	Clinical consequences	References
sirolimus	CYP3A4/5 (Pgp)	Case report	2	Children with acute lymphoblastic leukemia (USA)	At least 2 days	na	High Cmin when patients had flu-like symptoms (fever and cough)	Toxicity events (seizure and mouth sore)	(Mizuno et al., 2019)
Immunosuppressant drugs (antiproliferative drug)									
mycophenolate sodium (enteric-coated)	UGT1A8/9	prospective observational study (PK analysis)	66 (666)	Kidney transplant adults (Germany)	na	na	Higher AUC _{0-12h} in patients with recurrent infections compared to patients without infections	na	(Sommerer et al., 2010)
mycophenolate mofetil	UGT1A8/9	prospective observational study (PK analysis)	46 (127)(15 with infection or gastrointestinal disease and 31 without)	Kidney transplant adults (Japan)	na	na	A trend towards higher AUC _{0-9h} in patients with infection or gastrointestinal disease compared to those without	na	(Okamoto et al., 2005)
Immunosuppressant drugs (calcineurin inhibitor)									
tacrolimus	CYP3A4/5 (Pgp)	prospective observational study (PK analysis)	30 (200) (11 with diarrhea and 9 controls)	Kidney transplant adult (Belgium)	na	na	Association between diarrhea and Cmin Increase of C/D between 90 and 360 min after intake. No change of Tmax and t1/2 Decrease by about 50% (± 50%) of intestinal Pgp activity during diarrhea	na	(Lemahieu et al., 2005)
tacrolimus	CYP3A4/5 (Pgp)	prospective observational study (PK analysis)	20 (na)	Kidney transplant adults (Japan)	from 2 to 4 weeks	na	Higher Cmin, AUC, and Cmax during episodes of diarrhea	na	(Sato et al., 2004)
tacrolimus	CYP3A4/5 (Pgp)	case report	2 (23)	Liver transplant adults (Japan)	from 2 to 4 weeks	na	Decrease of Cmin two weeks after 2 or 4 weeks of direct-acting antivirals administration for HCV infection	Dose increase adjustment between 25% and 50 %	(Smolders et al., 2017)
tacrolimus	CYP3A4/5 (Pgp)	case report	1 (13)	Liver transplant child (Japan)	na	na	Increase of Cmin by 100% after an episode of diarrhea with fever	na	(Maezono et al., 2005)
tacrolimus	CYP3A4/5 (Pgp)	case report	2 (7)	Liver transplant adults	na	CRP range: 70 to 236 mg/L	Increase of Cmin Increase of C/D by 92 to 141% after inflammatory events	na	(Bonnevile et al., 2020)
cyclosporine	CYP3A4/5 (Pgp)	retrospective observational study	6 (88)	Adult recipients of allogeneic stem cell transplant (France)	na	Peak IL-6 : 212.2 ± 56.8 UI/ml Peak CRP: 179.2 ± 12.5 mg/L Peak α1-acid glycoprotein : 2.59 ± 0.32 gm/L	Correlation between time of IL-6 peak and: -three-fold increase in blood [cyclosporine] -twofold increase in [AM1**]	Cyclosporine dose decrease between 25 and 50%	(Chen et al., 1994)
cyclosporine	CYP3A4/5 (Pgp)	case report	1 (10)	Liver transplant adult (Japan)	na	na	Increase of Cmin by 300% 24 hours after an episode of diarrhea with fever	na	(Maezono et al., 2005)
Triazole antifungals									
voriconazole	CYP2C19, CYP3A4	prospective observational study	34 (489)	Adult hematological and SOT patients (Netherlands)	na	Na	Increase of Cmin by 1.005321 ^N and decrease of [voriconazole-N-oxide] by 0.99775 ^N , with N being the difference in CRP units (expressed in mg/L)	na	(Veringa et al., 2017)

voriconazole	CYP2C19, CYP3A4	prospective observational study	22 (143)	Hematological adult (Netherlands)	na	CRP: 37 [12 - 75] mg/L IFN γ : 15 [10-29] pg/mL IL10: 35 [12-66] pg/mL IL1-RA: 34 [18-106] pg/mL IL1B: 9.5 [8.5-11] pg/mL IL6: 32 [12-80] pg/mL IL8: 54 [22-122] pg/mL TNF α : 26 [15-44] pg/mL	Independent association between Cmin and CRP, IL-6, and IL-8. Absence of association between Cmin and other cytokines	na	(Vreugdenhil et al., 2018)
voriconazole	CYP2C19, CYP3A4	retrospective observational study	67 (520)	Adult recipients of allogeneic stem cell transplant (Japan)	na	CRP: 32 [range: 1-200.1] mg/L	CRP \geq 4 mg/L identified as an independent factor of Cmin \geq 1 mg/L	na	(Yasu et al., 2017)
voriconazole	CYP2C19, CYP3A4	retrospective observational study	29 (260)	Adult recipients of allogeneic stem cell transplant (France)	na	CRP: 8 [3-24] mg/L	Independent positive association between Cmin and CRP Increase of 24% of Cmin for each 1-log decimal increase of CRP	na	(Gautier-Veyret et al., 2017)
voriconazole	CYP2C19, CYP3A4	retrospective observational study	113 (250)	Hematological adult (China)	na	CRP: 5.99 (range:3-171) mg/L IL1B: 0.03 (< 0.1-489.3) pg/mL IL6: 135.1 (1.98-2969.1) pg/mL IL18: 141.9 (5.7-1834.7) pg/mL TGF β 1: 1750.9 (37.5-37916) pg/mL IFN γ : 0.23 (< 0.3-24.5) pg/mL	Absence of association between Cmin and CRP Association between Cmin and: - IL-18 in patients with acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia - TGF β 1 in acute myeloid leukemia	na	(Mafuru et al., 2019)
voriconazole	CYP2C19, CYP3A4	retrospective observational study	50 (139)	Adult hematological and SOT patients (Netherlands)	na	CRP:67 [14-153] mg/L	Association between Cmin and CRP Simultaneous evolution of Cmin and CRP level at individual level	na	(Encalada Ventura et al., 2016)
voriconazole	CYP2C19, CYP3A4	retrospective observational study	128 (128)	Adult hematological and SOT patients (Netherlands)	na	CRP: 71 [15-152] mg/L	Independent positive association between CRP and Cmin For every 1-mg/L increase in the CRP, increase of 0.015 (CI 95%: 0.011-0.020) mg/L of Cmin. Simultaneous evolution of Cmin and CRP at individual level	na	(Van Wanrooy et al., 2014)
voriconazole	CYP2C19, CYP3A4	retrospective observational study	19 (101)	Adult hematological and SOT patients (Netherlands)	na	CRP: 76.6 (range: 5.0-279.0) mg/L	Correlation between CRP and: - Cmin - metabolic ratio Increase of 0.021 mg/L for Cmin for each increase of 1 mg/L of CRP	na	(Encalada Ventura et al., 2015)
voriconazole	CYP2C19, CYP3A4	retrospective observational study	63 (77)	Adult hematological and SOT patients (Japan)	na	CRP: 5.6 \pm 6.4 mg/L	Increased CRP identified as an independent predictor of C/D	na	(Dote et al., 2016)
voriconazole	CYP2C19, CYP3A4	retrospective observational study	65 (72)	na (Japan)	na	na	Independent association between CRP and: - first Cmin - metabolic ratio	na	(Nioka et al., 2017)
voriconazole	CYP2C19, CYP3A4	retrospective observational study	41 (41)	Heterogeneous immunocompromised patients (Japan)	na	CRP: 3.46 [1.36-7.57] mg/L	Correlation between CRP : - Cmin/D - metabolic ratio	na	(Naito et al., 2015)

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Table 3 (continued)

Pharmacological class and drug	Mains enzyme (transporter) involved	Study type	Patients number (plasma/blood samples)	Population study (country)	Duration of the phenoconversion	Concentration of inflammatory biomarkers	Pharmacokinetic consequences	Clinical consequences	References
voriconazole	CYP2C19, CYP3A4	case-control study	62 (62) (31 cases with Cmin \geq 4 mg/L** and 31 controls)	Hematological adults (France)	na	CRP: 188 [109–227.5] (case); 37 [13.2–83.0] mg/L (control)	Class of CRP (> 96mg/L) identified as the unique independent factor of overexposure**	na	(Gautier-Veyret et al., 2019)
voriconazole	CYP2C19, CYP3A4, FMO3	retrospective comparative study	27 children (11 < 12 years and 16 > 12 years)	Na (Netherlands)	na	na	Positive association between CRP and Cmin in child >12 years No association between CRP and Cmin in children < 12 years	na	(ter Avest et al., 2017)
voriconazole	CYP2C19, CYP3A4	case report	1 (11)	Hematological adult (France)	na	CRP range: 25 to 263 mg/L	Simultaneous evolution of CRP and Cmin during the follow-up of 60 days	na	(Truffot et al., 2018)
posaconazole	UGT1A4	prospective observational study	55 (511)	Hematological adult (Netherlands)	na	CRP: 23.5 [5–75] mg/L	No association between CRP and Cmin	na	(Märtson et al., 2019)
itraconazole	CYP3A4/5	retrospective observational study	42 (42)	Heterogeneous immunocompromised patients (Japan)	na	CRP: 0.12 [0.04–0.66] mg/L	No association between CRP and: - C/D - hydroxyitraconazole - metabolic ratio	na	(Naito et al., 2015)
Anti-asthmatic drugs									
theophylline	CYP1A2	retrospective comparative study	52 (na)	Children with asthma (Japan)	about 2 days	na	Increased incidence of CRP > 0.5mg/L or fever in patients with lower Cmin72 h/Cmin24 h compared to patients with higher Cmin72 h/Cmin24 h ratio	na	(Yamaguchi et al., 2000)
theophylline	CYP1A2	case report	11 (na)	Children with asthma (USA)	between 1 to 3 months	na	Increased Cmin during influenza infection	toxic symptoms (seizure, nausea/vomiting, headache) in 10/11 patients	(Kraemer et al., 1982)
theophylline	CYP1A2	case report	5 (na)	Children with asthma (USA)	na	nd	Increased t1/2 during acute viral infection	na	(Chang et al., 1978)
theophylline	CYP1A2	case report	1 (na)	Adult healthy volunteer (Canada)	na	nd	Doubled t1/2 during acute viral infection	na	(Fleetham et al., 1978)
Anti-malaria drugs									
quinine	CYP3A4	prospective study (PK analysis)	5 (na)	Adults with experimentally-induced malaria (USA)	na	body temperature: 38.1 \pm 0.2 °C	Increased exposure during experimentally-induced malaria	Symptoms of cinchonism during malaria	(Morgan et al., 2018; Trenholme, Williams, Rieckmann, Frischer, & Carson, 1976)
quinine	CYP3A4	prospective study (PK analysis)	73 (na) (51 infected patients and 22 controls)	Children with uncomplicated malaria (na)	na	na	Reduced CL, Vd during malaria and increased exposure during uncomplicated malaria episode	No adverse effect was recorded	(Morgan et al., 2018; Sabchareon, Chongsuphajaisiddhi, & Attanath, 1982)
quinine	CYP3A4	prospective comparative study (PK analysis)	38 (na) (25 cerebral malaria and 13 uncomplicated malaria)	Adults and children with malaria (Thailand)	na	na	Reduced CL, Vd during malaria (especially in cerebral malaria) compared to convalescence period	No adverse effect was recorded	(Morgan et al., 2018; White et al., 1982)
quinine	CYP3A4	prospective comparative study (PK analysis)	15 (na)	Adults with malaria (Thailand)	less than 7 days	body temperature: 38.4 \pm 1.2°C Parasitemia: 58100 [18600–183000] parasites/ μ L	Decreased CL and increased exposure during malaria episode compared to convalescence period	na	(Morgan et al., 2018; Supanaranond et al., 1991)

quinine	CYP3A4	prospective study (PK analysis)	16 (na)	Adult patients with severe or moderately severe malaria (Thailand)	na	body temperature: 38.4 [range: 37.0-40.1] °C parasitemia: 15054 [range: 44-346222] parasites/ μ L body temperature: 38.6 \pm 0.6 °C parasitemia: 33064 [range: 11250-58999] parasites/ μ L	Reduced Cl, Vd during malaria episode compared to convalescence period Reduced Cl, Vd and increased exposure during malaria episode compared to convalescence period	na	(Morgan et al., 2018; Pukrittayakamee et al., 1997)
quinine	CYP3A4	prospective study (PK analysis)	6 (na)	Adults and children with uncomplicated malaria (Nigeria)	na	body temperature: 37.2 [36.0-38.9] °C parasitemia: 2240 [39.0-44.5] parasites/ μ L	No adverse effect was recorded	(Babalola, Polaji, Ogunbona, Sowunmi, & Walker, 1998; Morgan et al., 2018)	
quinine	CYP3A4	prospective study (PK analysis)	22 (na)	Pregnant women (2 nd and 3 rd trimester) (Uganda)	na	body temperature and parasitemia identified as covariates affecting CL and bioavailability, respectively	No adverse effect was recorded	(Klopprogge et al., 2014; Morgan et al., 2018)	
Anti-viral drugs lopinavir	CYP3A4	retrospective observational study	8 (8)	COVID-19 adult patients	nd	CRP range: 1.6 to 184.7 mg/L	Correlation between Cmin and CRP	na	(Schoergenhofer et al., 2020)
lopinavir	CYP3A4	retrospective observational study	12 (30)	COVID-19 adult patients	nd	CRP range: 19.4 to 157.5 mg/L	High bound and unbound Cmin in COVID-19 patients compared to HIV patients	Diarrhea (n=6), nausea/vomiting (n=2)	(Gregoire et al., 2020)

AM: cyclosporine metabolites, C/D: concentration/dose ratio, Cmin: trough concentration, CYP: cytochrome, FMO: flavin-monoxygenase 3, na: not available, nd: not determined, IL-6: interleukin 6, Pgp: glycoprotein P, PK: pharmacokinetics, MPE: median predicted error, t1/2: elimination half-life, SOT: solid organ transplant, Tmax: time after dose to maximum concentration, TNF α : tumor necrosis factor α , Vd: volume of distribution.

Data are indicated as mean (interval confidence or SD) or median [25th-75th percentile or range].

*Clozapine therapeutic reference range: 350-600 ng/mL (Hiemke et al., 2018); ** Voriconazole therapeutic reference range: 1-4 mg/L.

significantly higher during episodes of diarrhea in kidney transplant patients and the Cmin of tacrolimus returned to its previous concentration 2 to 4 weeks later (Sato et al., 2004).

In a meta-analysis that included 66 population pharmacokinetic studies, CRP levels had no significant effect on the interpatient variability of tacrolimus pharmacokinetics, in contrast to CYP3A5 genotypes (Campagne, Mager, & Tornatore, 2019). However, CRP was investigated in less than 10% of the studies.

The tacrolimus Cmin and dose-normalized pharmacokinetic profile were higher for 11 renal transplant recipients experiencing an episode of infectious diarrhea than for nine renal transplant recipients without diarrhea. Intestinal glycoprotein P activity was decreased by approximately 50% in the patients with diarrhea, suggesting that persistent and severe diarrhea was associated with increased oral bioavailability of tacrolimus. In two cases of pediatric liver transplantation patients treated with either tacrolimus or cyclosporine, the blood concentration of these immunosuppressants nearly doubled 24 hours after an episode of diarrhea with fever. Following the remission of diarrhea, the cyclosporine Cmin returned to the concentrations observed before the diarrheal episode (Maezono et al., 2005).

The Cmax of cyclosporine correlated to those of IL-6 and CRP in six patients who received bone marrow transplants (Chen et al., 1994). Moreover, the CYP P450-mediated formation of cyclosporine metabolites decreased with inflammation until it was below the limit of detection (Chen et al., 1994).

In a prospective PK study, two children with acute lymphoid leukemia had unexpected elevated sirolimus concentrations after experiencing flu-like symptoms, such as fever and cough, for three days (Mizuno, O'Brien, & Vinks, 2019). The estimated clearance of sirolimus decreased by approximately 40% and 50% for the two patients, necessitating a dose reduction. A similar result was observed in a sirolimus PK study in patients with vascular anomalies (Mizuno et al., 2017). In patients with documented infection, sirolimus clearance dropped by approximately 50%, requiring a dose reduction.

Finally, in renal transplant patients, a higher mycophenolic acid (MPA) AUC 0-9 h (Okamoto et al., 2005) or AUC 0-12 h was observed in patients with infectious disease than in those without (Sommerer et al., 2010).

4.4. Antifungal drugs (see Table 3)

A first retrospective study conducted on 128 patients reported a significantly elevated voriconazole Cmin in patients with moderate or severe inflammation (defined by CRP levels between 41-200 mg/L and >200 mg/L, respectively). This association remained significant after adjustment for multiple covariables (gender, age, dose, route of administration, liver enzymes, and medications) (Van Wanrooy et al., 2014). Such a link between inflammatory status (assessed most often by CRP levels) and voriconazole pharmacokinetics was later confirmed in numerous retrospective cohorts (Dote et al., 2016; Encalada Ventura, Span, van den Heuvel, Groothuis, & Alffenaar, 2015; Gautier-Veyret et al., 2017; Mafuru et al., 2019; Naito, Yamada, Mino, & Kawakami, 2015; Niioaka et al., 2017; Ventura et al., 2016; Vreugdenhil et al., 2018; Yasu et al., 2017) and in one prospective mono-center study (Veringa et al., 2017). Moreover, several cases reporting a similar evolution of voriconazole Cmin and CRP levels during longitudinal follow-up illustrate the impact of acute inflammation on voriconazole exposure at the individual level (Truffot, Thiebaut-Bertrand, Chapuis, Stanke-Labesque, & Gautier-Veyret, 2018; Van Wanrooy et al., 2014; Ventura et al., 2016; Yasu et al., 2017). Although these studies were heterogeneous in terms of study population (solid organ transplants and hematological patients), biological markers of inflammation (CRP, IL-6, IL-18 levels), and voriconazole pharmacokinetic parameters (Cmin, metabolic ratio), most reported increased voriconazole exposure during acute inflammation (see Table 3). Only one study with a limited sample

size, performed on 11 children <12 years of age, did not show any impact of inflammation on voriconazole exposure (ter Avest et al., 2017).

Several authors have proposed models to predict the increase in the voriconazole C_{min} in response to inflammation (Encalada Ventura et al., 2015; Gautier-Veyret et al., 2017; Van Wanrooy et al., 2014; Ventura et al., 2016; Veringa et al., 2017). As only a limited number of patients were included in several studies (Encalada Ventura et al., 2015; Gautier-Veyret et al., 2017; Veringa et al., 2017), these models need to be validated in larger independent studies simultaneously investigating inflammatory status and pharmacogenetics. This is particularly important, as two studies have suggested that the impact of inflammation on the voriconazole C_{min} depends on the CYP genotype (Gautier-Veyret et al., 2017; Veringa et al., 2017). Moreover, severe inflammation may blunt the influence of pharmacogenomic markers (CYP2C19 phenotype or a combined genetic score integrating the CYP2C19 and CYP3A genotypes) on voriconazole exposure, as a case-control study identified severe inflammation (defined by a CRP > 96 mg/L) as the unique risk factor of voriconazole overdose, whereas pharmacogenetic markers did not have a significant impact in this study (Gautier-Veyret et al., 2019).

There is little data concerning other triazole antifungals. One prospective study conducted on 55 patients treated with posaconazole did not find any association between the posaconazole C_{min} and inflammation, assessed by CRP levels (Märtson et al., 2019). Similarly, itraconazole exposure did not appear to be related to inflammation, since the unique retrospective cohort published to date did not find any link between the itraconazole C_{min} and CRP levels (Naito et al., 2015).

4.5. Other drugs (see Table 3)

The results of additional studies also support the hypothesis of the inhibition of DMETs during acute infection. For example, increased concentrations of theophylline during acute viral illness (Chang, Lauer, Bell, & Chai, 1978; Fleetham, Nakatsu, & Munt, 1978; Khan & Khan, 2019; Kraemer et al., 1982; Yamaguchi et al., 2000) and of quinine in the early phases of malaria treatment (see review (Morgan et al., 2018)) have been reported. Very recently, two short reports described higher plasma concentrations of lopinavir in severe COVID-19 patients (Gregoire et al., 2020; Schoergenhofer, Jilma, Stimpfl, Karolyi, & Zoufaly, 2020) compared to those observed in HIV-infected patients and in relation to plasma CRP concentrations (Schoergenhofer et al., 2020).

5. Pharmacological consequences of inflammation-induced metabolic phenoconversion in patients with chronic inflammation

As for acute inflammation, an inhibitory effect of chronic inflammation on DMETs is expected. However, the contribution of inflammation in the variability of drug exposure is difficult to address in patients with chronic disease due to numerous confounders, such as chronic infection, ageing, physical inactivity, stress, or disturbed sleep, which may be associated with some chronic diseases (Furman et al., 2019) and polymedication.

5.1. HIV infection

Despite effective antiretroviral therapy, chronic and persistent inflammation is observed in HIV-infected patients. Inflammation-induced pharmacokinetic variability may thus have a significant clinical impact on antiretroviral therapy medication, as efficacy and toxicity are directly associated with drug exposure. Indeed, higher inflammatory biomarker concentrations have been described in HIV patients than uninfected adults and inflammation persists after the suppression of HIV-RNA by antiretroviral therapy (Neuhaus et al., 2010). Interestingly, a

recent study showed that the level of inflammatory markers varies with the level of adherence (Castillo-Mancilla et al., 2016).

CYP activity in HIV-infected patients has been assessed using phenotyping tests. Lower CYP3A4, CYP2D6, and N-acetyl transferase 2 activity (18%, 90%, and 53%, respectively) was observed in 17 HIV-infected adults relative to that in uninfected controls using caffeine, dextromethorphan, and midazolam tests (Jones et al., 2010). Conversely, no significant difference was found in CYP1A2 activity. In another study using midazolam, dextromethorphan, and digoxin as *in vivo* phenotyping tests, overall CYP3A activity was approximately 50% lower in HIV-infected patients than in healthy volunteers (30 vs 12 patients, respectively), whereas CYP2D6 activity was unchanged (Jetter et al., 2010).

An impact of inflammation on the pharmacokinetics of antiretrovirals mainly metabolized by CYP3A, would thus be expected. However, data in the literature are sparse. Decreased maraviroc and elvitegravir clearance has been observed according to inflammatory status (Seifert, Castillo-Mancilla, Erlandson, & Anderson, 2017). Co-administration of IL-2 with indinavir to nine HIV patients led to an 88% increase in the AUC of indinavir (Piscitelli et al., 1998). Conversely, no significant correlation was observed between atazanavir clearance and inflammation biomarker concentrations in 107 HIV patients (Venuto et al., 2018). Yet, in this later study, the effect of inflammation could have been blunted by the presence of the booster ritonavir, which is systematically associated with atazanavir to decrease its clearance. Further studies are thus required to better define the impact of inflammation on the pharmacokinetics, tolerance, and efficacy of antiretroviral treatment.

The inflammatory status of HIV-infected patients may also have an impact on the pharmacokinetics of non-antiretroviral drugs. However, no clinical data are currently available and the potential impact is yet to be investigated.

5.2. Metabolic disorders

Few studies are available for patients with metabolic disorders, but CYP-mediated drug clearance is likely to be reduced in type 2 diabetes. Studies performed on liver tissue from diabetic patients demonstrated a decrease in total CYP content (Sotaniemi et al., 2002), with diminished expression and activity of CYP3A relative to controls (Dostalek, Court, Yan, & Akhlaghi, 2011). In addition, the exposure of the CYP3A substrate nisoldipine is elevated in hypertensive diabetic patients (Marques, Coelho, Dos Santos, Geleilate, & Lanchote, 2002) and cyclosporine metabolite concentrations are lower in kidney transplant recipients with diabetes mellitus (Akhlaghi et al., 2012) than in controls. Although these data are concordant, the role of inflammation in such CYP down-regulation in diabetes has never been investigated. Recently, a prospective study using a cocktail of probe drugs showed a decrease of approximately 38, 46, and 45% of the mean metabolic activity for CYP3A, 2C19, and 2B6, respectively, in 38 patients with type 2 diabetes relative to 35 controls (Gravel, Chiasson, Turgeon, Grangeon, & Michaud, 2019). Considering all diabetic and non-diabetic subjects, the IL-6 concentration significantly negatively correlated with the activities of CYP2B6, 2C19, and 3A in univariate analysis. Moreover, IFN- γ and TNF- α concentrations were identified as independent determinants of CYP2C19 and 2B6 activity (Gravel et al., 2019). These data all suggest that the inhibition of CYP-mediated drug clearance in type 2 diabetes may be related to inflammatory processes. However, these findings must to be confirmed, as the controls of these studies were often not well matched in terms of age, sex, or body mass index (Akhlaghi et al., 2012; Gravel et al., 2019; Marques et al., 2002).

Nonalcoholic fatty-liver disease (NAFLD) is associated with alterations of DMET expression and activity in experimental murine models and patients (see review (Cobbina & Akhlaghi, 2017)). This translates into increased midazolam exposure and an increased AUC of the glucuronide metabolites of morphine and acetaminophen via the

upregulation of the MRP3 efflux transporter. However, these results are limited and sometimes conflicting and need to be further investigated.

5.3. Chronic kidney disease (CKD)

The principal consequence of CKD on drug pharmacokinetics is a decrease in renal clearance. However, an impact of CKD on non-renal clearance has also been observed in many studies. Decreased CYP2C11, 3A1, 3A2, and N-acetyl transferase activity has been observed in non-clinical studies, whereas no modification was observed in CYP 1A1, 2B1, 2C6, and UDP-GT activity (Naud, Nolin, Leblond, & Pichette, 2012). In clinical studies, decreased non-renal clearance has been observed for numerous drug substrates of metabolizing enzymes (Nolin, 2008). Uremic factors (such as parathyroid hormone) that accumulate in end stage renal disease were identified as the main factors that contribute to varying non-renal clearance. Indeed, uremic factors decrease the mRNA expression and thus activity of drug-metabolism enzymes (Naud et al., 2012). As a systemic inflammatory response is observed in CKD patients (Stenvinkel, 2006), inflammatory factors may also be involved in reduced CYP activity. However, data are still lacking to accurately describe the impact of each factor in this multifactorial change. The impact of inflammation on CKD patients has been independently investigated in only one study, using alprazolam as a probe drug for CYP3A4 activity (Molanaei et al., 2018). The ratio of alprazolam to 4-hydroxyalprazolam correlated with CRP concentrations in 26 hemodialysis patients, suggesting the downregulation of CYP3A4 activity by inflammation.

5.4. Cancer

CRP concentrations positively correlate with weight loss, anorexia-cachexia syndrome, extent of disease, and recurrence in advanced cancer (Mahmoud & Rivera, 2002). Rivory et al. evaluated hepatic CYP3A activity using the phenotypic ¹⁴C-erythromycin breath test in cancer patients with CRP > 10 mg/L. They showed a mean 30% decrease in CYP3A activity relative to that in patients without an acute-phase response (Rivory, Slaviero, & Clarke, 2002). In patients with advanced cancer, docetaxel pharmacokinetics were the only predictive factor for hematological toxicity. The odds of severe hematological toxicity were approximately nine-fold higher for patients with reduced docetaxel clearance. The odds of non-hematological toxicity were approximately three-fold higher for patients with elevated orosomucoid or CRP concentrations (>1.5 g/L and >10 mg/L, respectively) (Charles et al., 2006).

5.5. Autoimmune inflammatory diseases

Studies performed in patients with rheumatoid arthritis or Crohn's disease support the hypothesis that inflammation contributes to the inhibition of drug metabolism. For example, higher exposure of verapamil in patients suffering from rheumatoid arthritis (Mayo, Skeith, Russell, & Jamali, 2000) or Crohn's disease (Sanaee et al., 2011) than controls has been reported. In addition, rheumatoid arthritis patients exhibit higher plasma concentrations of simvastatin, another CYP450 substrate (Schmitt, Kuhn, Zhang, Kivitz, & Grange, 2011) and lower plasma concentrations of 4-βhydroxycholesterol, an endogenous CYP3A4 metabolite (Wollmann et al., 2017). CYP3A4 activity has been shown to correlate with proinflammatory cytokine levels, especially those of IL-1ra, IL-6, and CXCL8 (Wollmann et al., 2018). In addition, the central role of IL-6 in the inhibition of CYP clearance in rheumatoid arthritis has been shown in clinical trials evaluating monoclonal antibodies targeting IL-6 (Lee, Tripathi, & Morgan, 2017; Schmitt et al., 2011; Zhuang et al., 2015). Indeed, these studies all showed that pharmacological inhibition of IL-6 restored CYP3A activity, with a significant decrease in simvastatin exposure of approximately 55 and 57% after the administration of sarilumab (Lee, Daskalakis, et al., 2017) or tocilizumab

(Schmitt et al., 2011), respectively. Conversely, several other biotherapies targeting proinflammatory cytokines, such as TNF-α (Deng et al., 2018; Frye, Schneider, Frye, & Feldman, 2002), IL-17 (Bruin et al., 2019), or IL-23 (Khalilieh et al., 2018; Khatri et al., 2019) did not influence CYP activity. However, any effect of such biologics needs to be verified for various diseases with varying levels of proinflammatory cytokines, as the magnitude of these disease-dependent drug interactions are *per se* affected by the underlying disease.

5.6. Liver disease and liver transplant

In chronic liver disease, most studies have focused on the impact of liver impairment on pharmacokinetics and inflammation is thus difficult to investigate as an independent factor of pharmacokinetic variability. UDP-GT mRNA levels were compared between liver biopsies of patients with low and high fibrosis or inflammation scores. Lower hepatic UDP-GT mRNA levels were observed in biopsies from patients with a high inflammation score, but not in those from patients with a high degree of fibrosis (Congiu, Mashford, Slavin, & Desmond, 2002). Some clinical data are available on chronic hepatitis C and B infections, in which chronic and persistent inflammation can be observed, such as in HIV infection. Morcos et al. investigated the impact of hepatitis C infection in chronically infected patients without liver impairment using midazolam as *in vivo* probe substrate. The midazolam metabolic ratio was lower in treatment-naïve patients (n = 35) and interferon null-responders (n = 24) than in healthy volunteers (n = 107), suggesting lower CYP3A4 activity in chronic hepatitis C patients (Morcos et al., 2013). In another study, lidocaine and its metabolite monoethylglycinexylidide (MEGX) were used as probe substrates of CYP activity in hepatitis C virus-positive cirrhotic patients with *Helicobacter pylori* gastric infection (Giannini et al., 2003). The mean MEGX concentrations were significantly lower in *Helicobacter pylori* infected than non-infected patients, independently of the Child-Pugh classification. These results suggest an impact of infection-induced inflammation on lidocaine metabolism. Unfortunately, data on the inflammatory factor concentrations were not available for these two studies. A decrease of 68% in CYP1A activity was also observed in 41 chronic hepatitis B patients (Wang et al., 2010).

Inflammation is observed during liver regeneration in living-donor liver transplantation and could affect drug metabolism in both donors and recipients (Li et al., 2016). However, no data are currently available to confirm this hypothesis.

6. How to integrate the inflammatory status in personalized medicine?

Inflammation reduces clearance by certain CYP and phase 2 enzymes, translating into the phenoconversion of intra-individual metabolic capacities. In particular, phenoconversion for extensive-metabolizer patients results in the change of a genotypic extensive-metabolizer into a phenotypic poor-metabolizer, leading to genotype-phenotype mismatches and an unpredictable increase in pharmacokinetic exposure to drugs that are DMET substrates, a drastic decrease in pharmacokinetic exposure to the corresponding metabolites, or reduced activity of pro-drugs. The clinical significance in terms of efficacy and safety of phenoconversion depends on whether the drug and/or its metabolites support the pharmacodynamic activity and their therapeutic index. In addition to extrinsic factors, including drug-drug interactions (see previous review (Shah & Smith, 2015)) or food/drug interactions, inflammation is an important intrinsic factor that can cause metabolic phenoconversion. Thus, unlike genotype, the pharmacokinetic phenotype of a subject is dynamic and inflammation-induced phenoconversion can transiently blunt the pharmacogenotype.

*Opinion: With the exception of pharmacogenotypes that contraindicate the use of certain drugs (HLA-B*5701 for abacavir, TPMT for azathioprine), genotype-guided dosing should be tempered by the inflammatory status of*

the patient. In hematological patients for example, severe inflammation has been shown to be the only independent predictor of voriconazole overexposure, whereas pharmacogenetic biomarkers had no significant impact (Gautier-Veyret et al., 2019). When interpreting a pharmacogenotype, pharmacologists should alert clinicians that severe inflammation can temporarily blunt a DMET genotype and the dose adjustment should account for the inflammatory status of the patient.

Experimental and clinical studies have showed that the impact of inflammation depends on different CYP isoforms (see Tables 2 and 3). Most data agree to suggest that inflammation is associated with inhibition of CYP1A, CYP3A, CYP2C9 and CYP2C19, which results in increased exposure of their respective substrates. Several studies have shown that plasma CRP concentrations mirror CYP substrate concentrations, such as those of voriconazole (Encalada Ventura et al., 2015) and tacrolimus (Bonneville et al., 2020). Others have reported an association between high CRP levels and overexposure to voriconazole (Gautier-Veyret et al., 2019), clozapine (Pfuhlmann et al., 2009), or risperidone (Hefner et al., 2016). For voriconazole, the CRP concentration is an independent predictor of the voriconazole C_{min} (Gautier-Veyret et al., 2017) and the voriconazole C_{min} correlates with the CRP level (Encalada Ventura et al., 2015; Naito et al., 2015; Van Wanrooy et al., 2014). In most studies, metabolic phenoconversion-induced drug overexposure occurred mainly in the presence of severe inflammation (CRP > 96 mg/l for voriconazole (Gautier-Veyret et al., 2019), CRP = 300 mg/l for midazolam (Vet et al., 2012)), CRP = 19.4 to 157.5 mg/l for lopinavir (Gregoire et al., 2020)).

The impact of inflammation is less evident on CYP2D6. Limited or heterogeneous effects of inflammation on the regulation of CYP2D6 have been reported in experimental animal models (Chaluvadi et al., 2009; Dickmann et al., 2012; Gwak et al., 2020; Nyagode et al., 2014) and discordant results regarding the activity of CYP2D6 have been observed in HIV-infected patients (Jetter et al., 2010; Jones et al., 2010). Moreover, in patients with psychiatric disorders, risperidone exposure (which is metabolized through CYP2D6) was increased in case of inflammation, while venlafaxine, another CYP2D6 substrate was not (Hefner, Shams, 2015). These clinical data are also consistent with the great interindividual variability of the metabolism mediated by CYP2D6 due to genetic polymorphisms.

A small number of clinical studies have suggested an inhibitory effect of inflammation on UDP-GT activity. Higher exposure to MPA was observed in renal transplant patients with infectious disease than in patients without (Okamoto et al., 2005). Conversely, the pharmacokinetics of the UDG-GT substrate posaconazole was not influenced by the inflammatory status. These data suggest that, the effect of inflammation may vary according to the UDP-GT subfamily, as for CYP.

Lastly, the impact of inflammation on drug exposure may also depend on the importance of drug metabolism in the total clearance of the drug, the contribution of CYP or UDP-GT family members in this metabolism, and their genetically-determined basal activities. The different effect of inflammation on MPA and posaconazole metabolism could for example be explained by the fact that 90 to 99% of the dose of MPA is metabolized by UDP-GT1A9 (Bullingham, Nicholls, & Kamm, 1998), whereas only 15 à 17% of the dose of posaconazole is metabolized by UDP-GT1A4 (Krieter et al., 2004).

Opinion: The impact of inflammation on drug exposure differs according to the drugs and TDM could help to measure pharmacokinetic variability. In parallel to TDM, monitoring CRP concentrations or checking for fever may be helpful to explain the occurrence of systemic overexposure of drugs metabolized by CYP1A2 (clozapine, theophylline), CYP3A (voriconazole, tacrolimus, everolimus, ciclosporin, midazolam, perampnenel, quinine, lopinavir) or type 2 enzymes (mycophenolic acid) when a drug/drug interaction with an inhibitor can be ruled out.

Concerning the transcriptional inhibitory effect of inflammation on DMETs, an increase in plasma CRP concentrations may precede an increase in CYP substrate plasma/blood concentration. The increase of this routine biomarker of inflammation should alert pharmacologists and clinicians to

the increased risk of overdose of DMET substrates with a short elimination half-life. Clinical care and TDM should be reinforced in this context.

The clinical consequences of inflammation-induced metabolic conversion are heterogeneous. Overexposure to theophylline or clozapine in association with acute inflammatory episodes has been associated with concomitant clinical signs of drug-related toxicity, whereas the immediate clinical consequences of increased exposure to voriconazole, tacrolimus, or risperidone associated with inflammation have not been documented (see Table 3). These data confirm that the inhibitory effect of inflammation on CYP may vary according to the CYP subfamily as previously discussed. *In vitro* hepatocyte experiments have shown that the potency of IL-6 to inhibit CYP was the strongest towards CYP1A2 relative to other CYPs (Dickmann et al., 2011). Since theophylline and clozapine are CYP1A2 substrates, the particular potency of IL-6 to inhibit CYP1A2 could explain the onset of theophylline or clozapine toxicity during acute episodes of inflammation.

Although the metabolic phenoconversion induced by inflammation may not be associated with short-term clinical signs of toxicity for other drugs (tacrolimus, voriconazole, risperidone), acute inflammation can also contribute to the increase in intra-individual variability of drugs that are CYP substrates, possibly leading to deleterious long-term consequences. For example, increased intra-individual variability of the tacrolimus blood C_{min} is associated with a poorer clinical outcome in hepatic transplant patients (Rayar et al., 2018). Moreover, it should also be kept in mind that total plasma drug concentration (free concentration + bound concentration) are measured during TDM or in most clinical studies (see Table 3). Certain drugs have strong binding affinity (>98%) for orosomucoid, the concentration of which is increased during acute inflammation (see Table 1). Thus, in a context of severe inflammation, the increased plasma total concentration of a drug highly bound to orosomucoid mainly reflects increased bound concentration. For example, correlations between orosomucoid concentration and risperidone +9-OH risperidone or lopinavir exposures have been described in a schizophrenic patient with pneumonia (Helland, Habib, Ulvestad, & Spigset, 2018) or in patients with severe HIV disease respectively (Ofotokun et al., 2011). Since the bound concentration of a drug does not support its pharmacological activity, this could contribute to explain the absence of clinical signs of toxicity in some situations, although a total overexposure is measured (Helland et al., 2018).

Opinion: When overexposure to a drug that is a DMET substrate with a narrow therapeutic index occurs in the context of acute infection, a treatment adaptation of this drug should not be systematically recommended. Pharmacologists should also take into consideration the pharmacokinetic properties of the drug, including its binding to orosomucoid, the importance of the different metabolic pathways involved in its clearance, and its terminal elimination half-life. For drugs highly bound to plasma proteins, a dose reduction could sometimes lead to loss of efficacy. But if adverse effects are observed, pharmacologists can suggest the brief discontinuation of treatment rather than dose reduction to avoid secondary underexposure upon the resolution of inflammation.

The resolution of an acute inflammatory episode is a complex physiological process, depending on the trigger of inflammation, and no study has investigated the duration of its resolution. This lack of data is a strong limitation for proposing dose reduction of DMET substrates to avoid consequent pharmacokinetic underexposure, notably for drugs with a narrow therapeutic window.

Opinion. As no studies have investigated the duration of the metabolic phenoconversion induced by inflammation, the combination of TDM and CRP monitoring may be useful to prevent drug underexposure when the inflammation episode is resolved.

Several case reports have suggested the repression of DMET inhibition at the resolution of the inflammatory episode, leading to reduced exposure of the DMET substrate in the context of chronic inflammation. The tacrolimus blood concentration decreased in two HCV-infected and liver-transplanted patients during treatment with daclatasvir/sofosbuvir/ribavirin (Smolders et al., 2017). Since a direct drug/drug

interaction between the direct-acting antivirals, ribavirin and tacrolimus, could be excluded, this study suggested that the unexpected observed decrease in the tacrolimus blood concentration when the sustained virological response was achieved could have been the consequence of the resolution of the HCV infection (Smolders et al., 2017).

Opinion. A potential impact of inflammation needs to be considered when unexpected variations in the blood concentrations of a DMET substrate occur in the absence of direct drug/drug interactions.

Treatment of rheumatoid arthritis patients with the monoclonal anti-human IL-6 receptor antibody tocilizumab (Schmitt et al., 2011) or sarilumab (Lee, Tripathi, & Morgan, 2017) normalized plasma CRP levels within one week after infusion and reduced simvastatin plasma exposure by 43 and 54%, respectively. These data suggest that blockade of the IL-6-dependent pathway reversed the suppression of CYP3A4 activity induced by inflammation and confirm the key role of IL-6 in the downregulation of CYP activity. Conversely, the anti-human IL-17A monoclonal antibody sekukinumab failed to modify the pharmacokinetic profile of midazolam in patients with moderate to severe psoriasis (Bruin et al., 2019). Similarly, the anti-human IL-23 antibody risankizumab did not affect the *in vivo* activity of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A in patients with moderate plaque psoriasis (Khatri et al., 2019). However, systemic inflammation was minimal in these study populations.

Opinion. In patients with severe chronic systemic inflammation, treatment with IL-6 monoclonal antibody (tocilizumab or sarilumab) reverses the suppression of CYP activity induced by inflammation. This requires intensification of clinical laboratory monitoring of DMET substrate drugs over the first week of treatment at least and, if underexposure is detected, increasing the dose so as to avoid loss of efficacy.

The impact of chronic or acute inflammation on drug pharmacokinetics has been studied using population pharmacokinetic models in only a few studies including inflammation factors as covariates. However, this methodology is probably a good approach to evaluate the impact of inflammation on pharmacokinetics and metabolism as an independent factor of variability. As previously described, inflammation is one of the many factors (demographic, genetic, pathological, etc.) that influences drug pharmacokinetics. Pharmacokinetic population studies could allow identification of the contribution of inflammation in inter-individual variability relative to that of other covariates, such as disease severity or glomerular filtration rate. Studying the relationship between inflammation and drug pharmacokinetics could also be helpful in adapting treatment, taking into account the limitation of the large intra-individual variability observed due to the inflammation status.

Opinion: Inflammation biomarkers (such as CRP) must be included in population pharmacokinetic studies as potential covariates, like renal or hepatic function biomarkers, especially for highly metabolized drugs.

7. Conclusion

Compelling evidence suggests that inflammation is a major regulator of DMETs and thereby contributes to intra- and interindividual pharmacokinetic variability of DMET substrates. The inhibitory effect of inflammation likely depends on its severity and the contribution of DMETs in the intrinsic clearance of a drug. However, the concentrations of the inflammatory biomarkers that inhibit the activity of each DMET are yet to be determined. This is essential in preventing overexposure to drugs that are DMET substrates, particularly concerning the ageing population and patients with a high prevalence of inflammatory comorbidities, including acute infections, and requires further studies. Studies aiming to investigate the genotype-predicted phenotype should also take into account the inflammatory status of patients to avoid misinterpretation, as the phenoconversion induced by inflammation may blunt the impact of genetic polymorphisms on drug pharmacokinetics and responses. As for genotype, demographic data, drug-drug interactions, and inflammatory biomarkers should be systematically taken into consideration for the personalization of drug treatment.

Submission Declaration

The authors state that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its submission is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. If accepted, it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the copyright-holder.

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Declaration of Competing Interest

All authors state they have no actual or potential conflict of interest including any financial, personal or other relationships with individuals or organizations within three years of initiating the work that could inappropriately influence, or be perceived to influence, the study design or data interpretation.

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