Influence of Inflammation on Cytochromes P450 Activity in Adults: A Systematic Review of the Literature

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Background: Available in-vitro and animal studies indicate that inflammation impacts cytochromes P450 (CYP) activity via multiple and complex transcriptional and post-transcriptional mechanisms, depending on the specific CYP isoforms and the nature of inflammation mediators. It is essential to review the current published data on the impact of inflammation on CYP activities in adults to support drug individualization based on comorbidities and diseases in clinical practice.

Methods: This systematic review was conducted in PubMed through 7th January 2021 looking for articles that investigated the consequences of inflammation on CYP activities in adults. Information on the source of inflammation, victim drugs (and CYPs involved), effect of disease-drug interaction, number of subjects, and study design were extracted.

Results: The search strategy identified 218 studies and case reports that met our inclusion criteria. These articles were divided into fourteen different sources of inflammation (such as infection, autoimmune diseases, cancer, therapies with immunomodulator...). The impact of inflammation on CYP activities appeared to be isoform-specific and dependent on the nature and severity of the underlying disease causing the inflammation. Some of these drug-disease interactions had a significant influence on drug pharmacokinetic parameters and on clinical management. For example, clozapine levels doubled with signs of toxicity during infections and the concentration ratio between clopidogrel’s active metabolite and clopidogrel is 48-fold lower in critically ill patients. Infection and CYP3A were the most cited perpetrator of inflammation and the most studied CYP, respectively. Moreover, some data suggest that resolution of inflammation results in a return to baseline CYP activities.

Conclusion: Convincing evidence shows that inflammation is a major factor to be taken into account in drug development and in clinical practice to avoid any efficacy or safety issues because inflammation modulates CYP activities and thus drug pharmacokinetics. The impact is different depending on the CYP isoform and the inflammatory disease considered. Moreover, resolution of inflammation appears to result in a normalization of CYP activity. However, some results are still equivocal and further investigations are thus needed.

Keywords: inflammation, cytochrome P450, pharmacokinetic, disease-drug interaction, cytokines
INTRODUCTION

Cytochromes P450 (CYP) are the major drug-metabolizing enzymes (DME) responsible for 75% of drug metabolism, making them decisive in the efficacy and safety of drugs (Wienkers and Heath, 2005). The interindividual variability in CYP activity is influenced by genetic factors, environmental factors and comorbidities (Lynch and Price, 2007). CYP genetic polymorphisms are well described, resulting in major functional differences (Zhou et al., 2017). CYP are also impacted by drug-drug interactions (DDIs) and several widely used drugs were removed from the market because of serious adverse drug reactions (ADRs) due to DDIs via the CYPs (Wilkinson, 2005). Therefore, the Food and Drug Administration (FDA) requires in-vitro evaluation of potential DDIs during the course of drug development (Kato, 2020; Food and Drug Administration).

A less well described but increasingly studied source of modulation of CYP activity and recently reviewed is that of endogenous inflammatory markers (de Jong et al., 2020; Stanke-Labesque et al., 2020). Inflammation is a response to endogenous or exogenous aggression that can be acute or chronic. It is prominent in many diseases, such as infection, trauma, surgery, arthritis, asthma, atherosclerosis, autoimmune disease, various immunologically mediated and crystal-induced inflammatory conditions, diabetes and cancer, to name a few (Gabay and Kushner, 1999; Germolec et al., 2018; Stavropoulou et al., 2018). This universal protective response involves innate and adaptive immunity and is present in virtually all tissues. Acute changes can be associated with variation in the concentrations of several plasma proteins, the acute-phase proteins (APP), and numerous behavioral, physiological, biochemical and nutritional changes (Gabay and Kushner, 1999). Cytokines are the main stimulators of APP production, and interleukin-6 (IL-6) is the key stimulator of APP while other cytokines (IL-1β, Tumor Necrosis Factor α, interferon-γ, transforming growth factor β and possible IL-8) influence APP subgroups (Gabay and Kushner, 1999). Thus, inflammation is a complex and well-orchestrated process involving many cell types and molecules that function as a cascade network, some of which initiate, amplify or sustain the process and others attenuate or resolve it (Gabay and Kushner, 1999; Stanke-Labesque et al., 2020).

Inflammation can impact drug PK through multiple mechanisms which typically occur in the liver, kidney, or intestinal epithelial cells (Stavropoulou et al., 2018; de Jong et al., 2020; Stanke-Labesque et al., 2020). The metabolic activities of CYPs are suppressed by inflammation in most cases, but some CYPs may be induced or remain unaffected (Morgan, 2001; de Jong et al., 2020; Stanke-Labesque et al., 2020). The positive and negative control of gene transcription is generally achieved by the interaction of regulatory proteins with specific DNA sequences on the regulated genes (Morgan, 1997). The impact of inflammation on the metabolic activity of CYPs has been studied in various in-vitro and animal models of inflammation, including trauma, infection and administration of endotoxin or cytokines (de Jong et al., 2020; Stanke-Labesque et al., 2020). Information available in the literature suggests that this impact on PK is triggered by cytokines and their intracellular signaling, directly or via interaction with the nuclear receptor pathway, on drug transporters and metabolizing enzymes (Liptrott and Owen, 2011; de Jong et al., 2020; Stanke-Labesque et al., 2020). Importantly, no single common pathway has been identified to explain the changes in the entire CYP family and involves different mediators but also different transcription factors (Renton, 2005; de Jong et al., 2020; Stanke-Labesque et al., 2020). Different effects of cytokines are observed in different cell types, which could be explained by a difference in the way intracellular signals from cytokine receptors are generated (Liptrott and Owen, 2011). Different cytokines exhibit a widely different spectrum of activity trough individual CYP isoforms and many different transcription factors (Morgan, 1997; Ruminy et al., 2001; Renton, 2005; Liptrott and Owen, 2011). Their activation by cytokines have been implicated in the downregulation and transcriptional regulation of different CYP isoforms (Morgan, 1997; Ruminy et al., 2001; Renton, 2005; Liptrott and Owen, 2011). Regulation of CYP during inflammation can occur through pre- and post-transcriptional mechanisms that are cytokine and CYP specific (de Jong et al., 2020; Stanke-Labesque et al., 2020).

Pre-transcriptional mechanisms currently described in the literature include transcriptional downregulation of transcription factors, interference with dimerization/translocation of (nuclear) transcription factors, altered liver-enriched C/EBP signaling, and direct regulation by NF-κB (de Jong et al., 2020). Overall, three main mechanisms have been described to explain the downregulation of inflammation in drug metabolizing enzyme and transporters expression and activity, namely inhibition of drug metabolizing enzyme transcription, epigenetic modifications in genes as a result of DNA methylation, modification of histone patterns, release of microRNA and NO-dependent proteasome degradation, which is a post-transcriptional mechanism (Stanke-Labesque et al., 2020).

Therefore, the aim of this systemic review is to evaluate the impact of inflammation on CYP activity in the adult population.

METHODS

The method used to manage the literature search was based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The detailed PICOS framework (i.e., participants, interventions, comparisons, outcomes, study design) was used as follows: Participants: adults with source of inflammation, -Intervention: victim drugs and CYPs concerned, -Comparison: healthy adults or before the onset of inflammation or receiving treatment for inflammation -Outcomes: potential effect of interaction between inflammation and CYP activity, -Study design: clinical trials and case reports/series.

Database and Search Strategy

The literature search was performed in PubMed via MEDLINE, the database of biomedical publications, for studies and case reports/series until January 7, 2021. To expand it, we also
performed a manual search of references for potentially relevant articles. The keywords used were “inflammation”, “cytochrome P450”, “cytochromes P450” and “CYP450.”

**Study Selection**

We applied the eligibility criteria described below in order to filter relevant publications from the total of results provided by the literature search.

The types of studies included in our literature search were randomized controlled trials, non-randomized studies, and observational studies, including case reports and series, published as full-text articles and congress abstracts in English. The year of publication selected was from database inception until January 7, 2021. Study participants had to be older than 18 years old, including healthy subjects and patients with an inflammatory...
condition, caused by disease, treatment or a medical or surgical procedure. The outcomes of interest were the effect of potential inflammation (suggested or provided) on metabolic ratios (MR) of CYP isoforms, the PK/PD and the safety profile of CYP substrates.

Successive steps in article selection included reading the title, abstract and full text according to the predefined eligibility criteria to screen for potentially relevant records. The selected articles were classified into literature reviews and in-vitro, animal, in-silico and human studies. Then, only studies involving adults (defined as over 18 years old) were kept, classified into studies or case reports/series. The same procedure was applied to assess the inclusion of additional articles identified by the manual search. The study selection process was summarized in a flowchart created according to the PRISMA statement requirements (Figure 1) (Moher et al., 2009).

Data Extraction and Management

Articles selected from the search results were collected and exported to the reference management software Zotero (version 5.0.85, © 2006–2018 Contributors) and merged to remove duplicates. Data from the included articles were extracted and synthesized. The authors extracted the following data according to the PICOS framework discussed above. These included study design, sample size, source of inflammation and comparators, victim drugs and CYP involved, and outcomes of interests (potential effect of interaction). When a CYP substrate was used in the article to determine whether or not inflammation or concomitant drugs altered its PK/PD profile, a verification of its metabolic pathway was performed. The verification process was performed using the Summary of Product Characteristics (SmPCs), the Lexi-Interact drug interaction checker and the Geneva table of CYP substrates, inhibitors, and inducers (Uptodate; Samer et al., 2013).

RESULTS

Identification and Selection of the Studies

The primary search, performed in PubMed, yielded a total of 2'283 articles that were screened according to their title and abstract. Of the remaining 523 articles, an additional 366 articles were identified by cross-referencing and handsearching of the reference list of the relevant articles (n = 889). Of these, 352 records were removed because the full text was not available (n = 128) or because they were considered irrelevant or not translated into English (n = 224). The remaining 537 articles were classified into review articles (n = 55), in-vitro (n = 77) or in-silico (n = 8) studies, and animal (n = 152) or human (n = 245) studies. The articles and case reports concerning the pediatric population (n = 27) are the subject of another systematic review and were excluded from this work (Lenoir et al., 2021). Finally, 218 articles conducted in adults were included and classified into studies (n = 180) and case reports/series (n = 38) for analysis (Figure 1).

Results of the Studies

The 218 eligible publications are summarized in Table 1 through 14. The drug-disease interactions found in the selected articles were divided into fourteen different sources of inflammation: unspecified source of inflammation (Table 1), infection (Table 2A), infection-example hepatitis (Table 2B), infection-example HIV (Table 3C), infection-example SARS-CoV-2 (Table 2D), vaccination (Table 3), kidney disease (Table 4), liver disease (Table 5), lung disease (Table 6), heart disease (Table 7), critically ill patients (Table 8), diabetes (Table 9), autoimmune diseases (Table 10), surgery (Table 11), cancer (Table 12), therapies with immunomodulator (Table 13) and therapies with anti-TNF-α and -mabs (Table 14). The most cited inflammation perpetrator was infection and the most studied CYP was CYP3A. CYP3A subfamilies refers to CYP3A4 and
CYP3A5, because the probe drugs used to assess the activity of CYP3A4 are metabolized by these two isoenzymes and no distinction can be made between them. Distribution in percent of all the references in the different categories are illustrated in Figure 2.

**Infection**

Several studies have assessed the association between infection, represented by elevated levels of CRP, and PK variations of voriconazole. This is of particular interest and voriconazole-induced metabolic phenoconversion (Stanke-Labesque et al., 2020). This is an important limitation to allow individualization of treatment without therapeutic drug monitoring (TDM), as under-exposure to drug remains a risk (Stanke-Labesque et al., 2020).

CYP downregulation was also demonstrated as a consequence of sufficient inflammation and significant temperature elevation (Elin et al., 1975). Therefore, caution should be exercised in case of infection when administering CYP substrates, as this may result in toxicity and ADRs (Voze et al., 1978; Blumenkopf and Lockhart, 1983; Levine and Jones, 1983; Levine and Jones, 1983; Raaska et al., 2002; Haack et al., 2003; de Leon and Diaz, 2003; Jecel et al., 2005; Darling and Huthwaite, 2011; Espnes et al., 2012; Abou Farha et al., 2012; Khan and Khan, 2019).

Early works assessed the effect of an infection induced intentionally by lipopolysaccharides (LPS) injection on antipyrine pharmacokinetics, and several studies have assessed the impact of infection on psychotropic agents (clozapine, risperidone). The increase of clozapine levels, a CYP1A2 substrate, due to inflammation has been well studied and demonstrated (Raaska et al., 2002; Haack et al., 2003; de Leon and Diaz, 2003; Jecel et al., 2005; Pfluhmann et al., 2009; Darling and Huthwaite, 2011; Espnes et al., 2012; Abou Farha et al., 2012; Leung et al., 2014; Kwak et al., 2014; Takahashi et al., 2015; Clark et al., 2018; Khan and Khan, 2019).

### Table 1: Impact of unspecified source inflammation on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-----------------------------|-------------------------------|-------------------|--------------------------------|-----------------------|
| IL-10 injection             | tolbutamide (CYP2C9), caffeine (CYP1A2), dextromethorphan (CYP2D6) and midazolam (CYP3A) | 12                | - significantly but moderately decreased CYP3A4 activity (12 ± 17%, p < 0.02) | Wenkers and Heath (2005) Double-blind crossover study |
| Elevated CRP levels (>1.5 mg/dl) | perampanel (CYP3A4) | 111 = Total 23 = CRP > 1.5 mg/dl 13 = enzyme-inducing AEDs 10 = no enzyme-inducing AEDs | - perampanel C/D increased by 53.5 and 100.8% respectively when CRP >1.5 mg/dl  - correlation between serum CRP level and C/D of perampanel (r = 0.44, p < 0.001) | Lynch and Price (2007) Cohort study |
| Erythrocyte sedimentation rate (ESR) > 20 mm vs. control | Oxprenolol (CYP2C9, 2D6, 3A4 and 1A2 substrate) | 18                | - mean oxprenolol AUC 2-fold greater in inflammation group | Zhou et al. (2017) Cohort study |
| CRP serum levels | tacrolimus (CYP3A4) | 31-year-old man | -tacrolimus C/D increased during two inflammation episodes by 54% (cholestasis) and 141% (infection following surgery), and strongly correlated with CRP (r = 0.78, p = 0.079) | Wilkinson (2005) case report |

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*References and design:*
- Wenkers and Heath (2005) Double-blind crossover study
- Lynch and Price (2007) Cohort study
- Zhou et al. (2017) Cohort study
- Wilkinson (2005) case report
| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|--------------------------------|--------------------|--------------------------------|-----------------------|
| Lipopolysaccharides (LPS)-induced inflammation | theophylline (CYP1A2), hexobarbital (CYP2C19) and antipyrine (CYP1A2, 2B6, 2C9, 2C19, 2C18 and 3A4) | 12 | - significant repression of CYPs activity (takes several hours to develop) | Kato (2020), Crossover study |
| Two injections of Gram-negative bacterial endotoxin | theophylline (CYP1A2), hexobarbital (CYP2C19) and antipyrine (CYP1A2, 2B6, 2C9, 2C18 and 3A4) | 9 | - significant decrease of clearances of all probes compared with the saline control studies, - endotoxins injections associated with decreased hepatic drug metabolism, mainly CYP1A2 and 2C19 | Food and Drug Administration, Cross-over clinical trial |
| Administration of a single oral dose of 10 mg/kg of etiocholanolone | antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 14 = significant fever (fever index >50) 19 = failed to develop significant fever (fever index <50) | - half-life was significantly prolonged (29.3%, p < 0.005) in patients with significant fever - no significant change of half-life (p > 0.8) in patients without significant fever | Cross-over clinical trial |
| Acute pneumonia | antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 14 | - 1.5 fold increased clearance 14 and 28 days after the acute illness - enhancement of clearance in 28 days represented a 36% improvement - 26% lower urine levels of 7-hydroxyantipyrine (7-HC) after praziquantel (p < 0.001) compared to initial assessment | Stanke-Labesque et al. (2020), Cohort study |
| Liver fluke infection (uninfected, infected only and infected with fibrosis) | coumarine (CYP2A6) | - Total = 91 | - infected individuals excreted slightly higher levels of 7-HC in the 0–2 h period - acute spinal subdural hematoma and subarachnoid haemorrhage during the course of a thoracic level infection - 3-fold increased PT times requiring vitamin K administration | Stavropoulou et al. (2018), Cohort study |
| Herpes zoster | warfarin (CYP2C9) | 66-year-old woman | - 73 completed the two assessments | Germolec et al. (2018), Case report |
| Visceral leishmaniasis | midazolam (CYP3A), omeprazole (CYP2C19), losartan (CYP2C9) | 24 | - significantly increased midazolam CL/F (p = 0.018) 2–3 days and 3–6 months after curative chemotherapy - significantly increased omeprazole CL/F (p = 0.008) 2–3 days and 3–6 months after curative chemotherapy - CYP2C9 activity not significantly different between controls and infected patients | Gabay and Kushner (1999), Cohort study |
| Influenza A | theophylline (CYP1A2) | 50-year-old woman | - toxicity symptoms after infection - increased theophylline levels (1.5x above normal values) | Morgan (2001), Case report |
| Acute illness | theophylline (CYP1A2) | 3 | - 2-fold or 3-fold variation in clearance during acute illness - clearance decreased during worsening of airway obstruction in one patient - 2 patients had increased clearance during the improvement of their condition (pneumonia and congestive heart failure) | Morgan (1997), Case series |
| Elevated CRP levels (>5 mg/L) vs control | citalopram (major CYP2C19, minor CYP3A4) and venlafaxine (major CYP2D6, minor CYP3A4 and 2C19) | 15 citalopram | - no statistical differences in citalopram and venlafaxine concentrations or in MR of both drugs in samples with elevated CRP levels | Liptrott and Owen (2011), Cohort study |
| Elevated serum levels of CRP | risperidone (bioactivated by CYP3A4 and CYP2D6) | 39 venlafaxine 2 females (56 and 38 years old) | - close temporal association between serum levels of risperidone active moiety (risperidone + 9-hydroxyrisperidone) and CRP - > 3x increase of C/D during elevated CRP serum concentration | Renton (2005), Case report |

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TABLE 2A | (Continued) Impact of infection on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|--------------------|-------------------------------|-----------------------|
| Pneumonia                     | risperidone (bioactivated by CYP3A4 and CYP2D6) | 56-year-old man | 5-fold higher risperidone dose requirement during pneumonia | Ruminy et al. (2001) |
| Elevated serum levels of CRP (>5 mg/L) | clozapine (CYP1A2), quetiapine (CYP3A4 and CYP2D6) and risperidone (CYP3A4 and CYP2D6) | 33 clozapine, 32 quetiapine, 40 risperidone | - C/D of clozapine was significantly higher (< 0.01) and CYP1A2 MR (NCLZ/CLZ) significantly lower (< 0.05) | Moher et al. (2009) |
| Elevated serum levels of CRP | clozapine (CYP1A2) | 27 high drug level | - positive and significant correlation between clozapine and CRP levels (r = 0.313, p < 0.01) | Uptodate |
| Elevated serum level of CRP of 130 mg/L | clozapine (CYP1A2) | 44-year-old man | - no difference in C/D or in MR of quetiapine | Case report |
| Elevated serum level of CRP of 256 mg/L | clozapine (CYP1A2) | 50-year-old man | - condition improved when treatment was discharged | Case report |
| Sepsis                        | clozapine (CYP1A2) | 61-year-old woman | - elevated clozapine levels | Case report |
| Suspected infections           | clozapine (CYP1A2) | 4 | - clozapine toxicity symptoms in usually stable patients | Dote et al. (2016) |
| Suspected infections           | clozapine (CYP1A2) | 62-year-old man | - clozapine levels increased during infection (from 377 ng/ml to 1'628 ng/ml) | Encalada Ventura et al. (2015) |
| Respiratory infection          | clozapine (CYP1A2) | 34-year-old man | - increased clozapine levels to 1245 ng/ml during infection | Case report |
| Lung abscess                   | clozapine (CYP1A2) | 29-year-old man | - increased clozapine levels during infection (from 681 ng/ml to 1'467 ng/ml) | Case report |
| Influenza A                    | clozapine (CYP1A2) | 33-year-old woman | - No signs of clozapine toxicity | Case report |
| Pneumonia                     | clozapine (CYP1A2) | 42-year-old man | - increased clozapine levels during infection (from 661 ng/ml to 1'300 ng/ml) | Case report |
| Pneumonia                     | clozapine (CYP1A2) | 35-year-old man | - symptoms of clozapine toxicity | Case report |
| Upper respiratory tract infection | clozapine (CYP1A2) | 68-year-old woman | - increased median clozapine C/D ratios at the peak of infection | Case report |

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TABLE 2A | (Continued) Impact of infection on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|--------------------------------|--------------------|--------------------------------|-----------------------|
| Upper respiratory tract infection | clozapine (CYP1A2) | 47-year-old man | - On day 24 and 25 (highest level of infection severity), serum concentration levels increased to 881.2 and 663.5 ng/ml, respectively | Schulz et al. (2019) |
| Urinary tract infection | clozapine (CYP1A2) | 51-year-old woman | - increased clozapine levels during infection (peak at 1'086 ng/ml) - patients improved after dose reduction and recovery | Case report |
| Urinary tract infection | clozapine (CYP1A2) | 45-year-old woman | - increased clozapine levels during infection (from 705 ng/ml to 2'410 ng/ml) - toxicity symptoms | Case report |
| Urinary tract infection | clozapine (CYP1A2) | 62-year-old man | - increased clozapine levels during infection (from 432 ng/ml to 1'192 ng/ml) - no toxicity symptoms | Case report |
| Urinary tract infection | clozapine (CYP1A2) | 64-year-old woman | - decreased clozapine levels after infection recovery (from 748.4 to 260.0 ng/ml) - toxicity symptoms | Case report |
| Infections | clozapine (CYP1A2) | 16 patients with 18 episodes | - only 2 episodes did not require any relevant changes of dosage | Case series |
| Infections | clozapine (CYP1A2) | 3 | - clozapine toxicity symptoms - 2.5-7-fold increased clozapine serum concentration during infections | Case series |
| Diarrheic stools and gastrointestinal bacterial infection | clozapine (CYP1A2) | 23 years old man | - at admission, CRP serum concentration = 130 mg/ml and clozapine serum concentration = 9074 nmol/L (References interval 200–2500 nmol/L) - 1 month before, serum concentration = 1919 nmol/L 1 month before admission and fairly constant during the last years - trough concentration = 2074 μg/L at day 0 (before any antibiotics treatments) - previous trough concentrations were three times lower - during the infection, CRP = 152 mg/L and α1-glycoprotein = 2398 mg/L - concentration decreased nearly to the previous levels after 2 weeks (624 ± 214 mg/L) | Case report |
| Bacterial pneumonia | clozapine (CYP1A2) | 53-year-old woman | - trough concentration = 2074 μg/L at day 0 (before any antibiotics treatments) | Khan and Khan (2019) |
| Increased CRP level | voriconazole (CYP3A4 and CYP2C19) | 63 | - increased CRP levels associated with significantly increased voriconazole C/D (p < 0.05) - CYP3A4 and CYP2C19 downregulated by inflammation | Retrospective study |
| Increased CRP level | voriconazole (CYP3A4 and CYP2C19) | 19 | - inflammatory response positively associated with voriconazole concentration (r = 0.62, p < 0.001) - inflammatory response negatively associated with voriconazole MR (rho = -0.64, p < 0.001) | Cohort study |
| Elevated CRP level | voriconazole (CYP3A4 and CYP2C19) | 54 | - voriconazole/N-oxide ratio could be predicted by the CRP concentration with a standardized regression coefficient of 0.380 (p = 0.001) | Cohort study |
| Elevated IL-6, IL-8 and CRP levels | voriconazole (CYP3A4 and CYP2C19) | 22 | - correlation between IL-6 (r = 0.46, p < 0.0001), IL-8 (r = 0.42, p < 0.0001) and CRP (r = 0.53, p < 0.0001) and trough concentration | Cohort study |

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| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|--------------------|-------------------------------|-----------------------|
| CRP serum level               | voriconazole (CYP3A4 and CYP2C19) | Total = 128        | - trough concentration increased by 0.015 mg/L every 1 mg/L increase in CRP  
- correlation between trough concentration and CRP levels (p < 0.001), and with severity of inflammation | Jecel et al. (2005) Retrospective study |
| - Elevated (>200 mg/L)        |                               |                    |                               |                       |
| - Moderate (>41 mg/L, <200 mg/L) |                              |                    |                               |                       |
| - Control (<40 mg/L)          |                              |                    |                               |                       |
| Multiple infections along his 5 months hospital stay | voriconazole (CYP2C19 and 3A4), meropenem and their combinations | 78-year-old man | - decreased voriconazole dose requirements | Darling and Huthwaite (2011) |
| CRP serum level               | voriconazole (CYP3A4 and CYP2C19) | 34                 | - MR significantly decreased with higher CRP concentration after adjustment (p < 0.001)  
20 = patients with CYP2C19 genotype performed | Espnes et al. (2012) Case report |
| CRP serum levels              | voriconazole (CYP3A4 and CYP2C19) | 31 with overdose  | - mean CRP level significantly higher (p < 0.0001) in patients who experienced an overdose (188 mg/L) compared to those who did not (37 mg/L)  
31 = without overdose | Levine and Jones (1983) Case-control study |
| CYP2C19 genotype              | CRP serum levels              | voriconazole (CYP3A4 and CYP2C19) and itraconazole (CYP3A4) | 41 voriconazole  
42 itraconazole | Raaska et al. (2002) Cohort study |
| CRP serum levels              | voriconazole (CYP3A4 and CYP2C19) | 64-year-old man | - voriconazole C/D associated with inflammation level | Clark et al. (2018) |
| Inflammation level            |                              |                    |                               |                       |
| Influenza-like illness        |                              |                    |                               |                       |
| Pneumonia                     |                              |                    |                               |                       |
| Inoculation of Malaria        |                              |                    |                               |                       |
| Infection disease state (pneumonia, endocarditis, wound infection or gastroenteritis vs healthy state) | tacrolimus (CYP3A) | 52 | - mean tacrolimus trough level 2.3 times higher during enteritis (p = 0.0175)  
- mean trough level returned to their baseline levels 2 weeks after onset | Pfühlmann et al. (2009) Cohort study | (Continued on following page)
Several studies have examined the impact of HIV on CYP metabolism (Table 2C) and have shown that several concomitant treatments and antiretroviral drugs metabolized by CYP3A have reduced metabolism in HIV-infected individuals, with an increased risk of ADRs. For instance, clindamycin clearance decreased from 0.27 in healthy volunteers to 0.21 L/h/kg in AIDS patients (p = 0.014) and a negative correlation between TNF-a and midazolam clearance was found (Gatti et al., 1993; Jones et al., 2010). Moreover CYP3A inhibitor (ketoconazole or ritonavir) and inducer (rifampicin) effects were less pronounced on antiviral PK in HIV-patients (Gatti et al., 1993; Grub et al., 2001; Jetter et al., 2010; European medicines agency; Packageinserts). It is important to characterize CYP3A modulation in HIV, as many antiviral treatments are metabolized by this pathway, and this could lead to efficacy or safety concerns. However, the AUC of atazanavir was lower in HIV-infected patients than in healthy volunteers and this could

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**Table 2A** (Continued) Impact of infection on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|------------------------------|-------------------------------|--------------------|---------------------------------|----------------------|
| Helicobacter pylori infection in cirrhotic patients | / | 21 tested positive and 11 not | Hp-infected cirrhotic patients had a significant lower mean of the monoethylglycinexylidide (MEGX) test compared to non-infected patients (p = 0.006), while 13C-galactose breath test (GBT) was not | Abou Farha et al. (2012) |
| Sepsis | tacrolimus (CYP3) | 41-year-old man | 151% increased tacrolimus C/D during sepsis | Case-control study Wilkinson (2005) |
| Dermatitis | clozapine (CYP1A2) | 57-year-old woman | On days 36 and 43 (highest level of dermatitis severity), clozapine serum concentration increased to 889.2 and 1012 ng/ml, respectively | Case report Schutz et al. (2019) |
### TABLE 2B | Impact of hepatitis on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction | References and design |
|--------------------------------|--------------------------------|--------------------|--------------------------------|-----------------------|
| Chronic hepatitis C           | antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 12 = chronic hepatitis C, 18 = controls | - decreased clearance and greater excretion in urine (about 50%, \( p < 0.01 \))<br>- no difference in hepatic enzymes levels but Child Pugh Score correlated with clearance (\( r = -0.73, p = 0.007 \)) | ten Bokum et al. (2015) Case-control study |
| Chronic hepatitis C           | antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 85                  | - no difference in clearance before and after 6 weeks of interferon treatment<br>- 14% clearance increased (\( p < 0.05 \)) 6 months later among responders but not in those who had failed to respond to interferon | Ruan et al. (2017) Cohort study |
| Acute viral hepatitis         | antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 6                   | - decreased plasma half-life and plasma clearance during the acute phase of hepatitis compared to recovery period (\( p < 0.02 \)) | Ruan et al. (2018) Cohort study |
| Acute hepatitis               | hexobarbital (CYP2C19)        | 13 = hepatitis, 14 = controls | - decreased elimination half-life in patients with hepatitis compared to controls (490 ± 186 min vs. 261 ± 69 min, \( p < 0.001 \)) | Ruan et al. (2020) Case-control study |
| Hepatitis C infection (IFN)   | Cyclosporin A (CyA) and tacrolimus (CYP3A4) | 26 = hepatitis C infection, 78 = controls | - Lower doses (\( p < 0.05 \)) in hepatitis C compared to controls, while levels were comparable | Sonne et al. (1985) Case-control study |
| Acute viral hepatitis C       | CyA (CYP3A4)                  | 18 = HCV Ab +, 18 = HCV Ab - | - CyA levels significantly higher in HCV Ab + (\( p = 0.0001 \))<br>- altered CyA PK (higher peak levels and drug exposure) in HCV+, especially those with viremia | Satana et al. (1996) Case-control study |
| Acute viral hepatitis C       | CyA (CYP3A4)                  | 11 = anti-HCV +, 11 = controls | - terminal plasma half-life significantly prolonged in acute viral hepatitis compared to controls (\( p < 0.001 \))<br>- 2-fold change in total plasma clearance observed (\( p < 0.002 \)) | Hanada et al. (2012) Case-control study |
| Acute viral hepatitis C       | CyA (CYP3A4)                  | 10 = anti-HCV +, 14 = controls | - CyA AUC 69% (\( p < 0.01 \)) and 32% (\( p < 0.01 \)) higher in pre- and post-transplant studies in HCV + patients | Hanada et al. (2012) Case-control study |
| Acute hepatitis               | meperidine (CYP2B6, 2C19 and 3A4) | 14 = acute viral hepatitis, 15 = controls | - total plasma clearance increased from 488 ± 132 ml/min to 1200 ± 555 ml/min and the terminal half-life decreased from 8.24 ± 3.71 to 3.25 ± 0.80 h respectively (\( p < 0.005 \))<br>- values after recovery were not significantly different from those of the control group | Latorre et al. (2002) Case-control study |
| Acute hepatitis               | meperidine (CYP2B6, 2C19 and 3A4) | 5                   | - total plasma clearance increased from 488 ± 132 ml/min to 1200 ± 555 ml/min and the terminal half-life decreased from 8.24 ± 3.71 to 3.25 ± 0.80 h respectively (\( p < 0.005 \))<br>- values after recovery were not significantly different from those of the control group | Latorre et al. (2002) Case-control study |
| Chronic hepatitis C (CHC)     | midazolam (CYP3A4)            | 107 = controls      | - MR decreased by 37 and 54% (\( p < 0.05 \)) in patients with hepatitis C treatment-naive and interferon null-responders respectively, compared to controls | Tuncer et al. (2000) Case-control study |
| Acute viral hepatitis C       | dextromethorphan (CYP2D6)     | 24 = CHC null responders to IFN | - consistent reductions in CYP3A4 activity between healthy volunteers and patients infected, most substantial difference with interferon null-responders | Wolfenbüttel et al. (2004) Case-control study |

(Continued on following page)
be explained by the absence of correlation between its oral clearance and inflammatory markers in a cohort study, the lack of identical study conditions (doses, sample schedule, meals ... etc.) between the two groups and the fact that HIV infection was well-controlled (Packaginserts; Le Tiec et al., 2005; Venuto et al., 2018). Indeed, caffeine metabolism was not altered in HIV-infected patient compared with healthy volunteers, but was decreased in AIDS patients (Lee et al., 1993; Jones et al., 2010). Moreover, atazanavir was administered with the booster ritonavir to decrease its clearance, and the effect of inflammation could have been minimized.

More recently, some studies have shown increased plasma concentration of CYPs substrates (mostly CYP3A) during SARS-CoV-2 infection, which may have led to believe that there was a CYPs downregulation due to inflammation (Table 2D) (Cojutti et al., 2020; Cranshaw and Harikumar, 2020; Gregoire et al., 2020; Smolders et al., 2017).

| Inflammation characterized by | Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|------------------------------|--------------------|-------------------------------|------------------------|
| Hepatitis A                   | coumarine (CYP2A6)           | 9 = hepatitis A    | - mean reduction of 37% (p < 0.05) of the total urine excretion | McHorse et al. (1975) |
|                               |                              | 20 = controls     | - CYP2A6 lower metabolic activity in hepatitis patients | Case-control study     |
| Hepatitis C virus (HCV) vs    | omeprazole (CYP2C19) and    | 31 = HCV (9 with chronic | - mean omeprazole hydroxylation index in HCV hepatitis and patients were significantly higher compared with healthy subjects, with lower CYP2C19 activity | Smolders et al. (2017) |
| control                       | cortisol (CYP3A)             | 22 with cirrhosis) | - mean clearance of cortisol decreased significantly (p < 0.001) in CLD patients | Case-control study     |
| Chronic HCV treated with     | tacrolimus (CYP3A)          | 56-year-old male  | - through concentration decreased after initiation of HCV treatment that required an increased dosage of | Kawaoka et al. (2016)  |
| sofosbuvir                    |                              |                   |                               | Case report            |
| HCV treated with             | tacrolimus (CYP3A)          | 74-year-old male  | - case 1: slight increase in trough blood concentration after the start of the combination therapy but no dose adjustment | Saab et al. (2016)     |
| daclatasvir/asunaprevir       |                              | 57-year-old man   | - case 2: through blood concentration decreased after the start of the combination therapy and dosage was increased | Case report            |
| HCV before and after         | tacrolimus (CYP3A) and      | 52                | - statistically significant difference in daily dose adjusted per weight or serum levels of tacrolimus after achieving a sustained viral response | Raschzok et al. (2016) |
| treatment                     | cyclosporine (CYP3A)        |                   | - no statistically significant difference in daily dose adjusted per weight or serum levels of cyclosporine after achieving a sustained viral response | Cohort study           |
| HCV treated with directly    | tacrolimus (CYP3A) and      | 21                | - mean LMAx increased from 344 ± 142 to 458 ± 170 μg/kg/h between the start of treatment and week 12 (p < 0.001) (value in healthy volunteers = 430 ± 86 μg/kg/h) | Ueda and Uemoto (2016) |
| acting antivirals             | 13C-methacetin (LMAx test,  |                   | - tacrolimus C/D decreased over the same period (p = 0.0017) | Cohort study           |
|                              | CYP1A2)                      |                   |                               |                        |
| HCV treated with             | tacrolimus (CYP3A)          | 10                | - C/D ratio decreased from 3.95 ng/ml per mg to 2,975 ng/ml per mg after 2 weeks of administration | van den Berg et al. (2001) |
| daclatasvir/asunaprevir       |                              |                   | - dose required to obtain therapeutic levels was comparable in the 2 groups during the first 3 weeks | Cohort study           |
| HCV                           | tacrolimus (CYP3A)          | 7 = HCV           | - dose requirement decreased sharply in HCV patients (20% of the value in controls) | Kugelmas et al. (2003) |
|                               |                              | 13 = transplanted for other indications | - dose requirement increased by more than 50% in 2 patients treated with IFN-αrabitivir | Cohort study           |
| HCV treated with             | tacrolimus (CYP3A) and      | 12 (7 cyclosporine and 5 | - cyclosporine and tacrolimus levels at baseline vs after HCV RNA negativation decreased significantly (p = 0.018 for cyclosporine and p = 0.044 for tacrolimus) | Ueda et al. (2015)     |
| anti-HCV therapy              | cyclosporine (CYP3A)        | 18 (7 cyclosporine and 11 tacrolimus) = non-responders | | Cohort study           |
| HCV treated with             | tacrolimus (CYP3A) and      | 2                  | - C/D ratio of calcineurin inhibitors were elevated in the first 2 weeks in both cases, but decreased thereafter, necessitating an increase in the dose | Morcos et al. (2013)   |
| simprevir                     | cyclosporine                 |                   |                               | Case report            |
| Inflammation characterized by | Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|--------------------|-------------------------------|-----------------------|
| AIDS patients vs control | clindamycin (CYP3A) | 16 = AIDS | - clearance values normalized to subject body weight were 0.27 ± 0.06 L/h/kg for the healthy volunteers and 0.21 ± 0.06 L/h/kg for the AIDS patients (p = 0.014) | Breimer et al. (1975) |
| | | | - ADR following administrations (same dose) were observed in eight patients with AIDS | Case-control study |
| | | 16 = healthy volunteers | | |
| | | | | |
| HIV-infected patients vs control | midazolam (CYP3A), dextromethorphan (CYP2D6) and caffeine (CYP1A2) | 17 = HIV-infected | - midazolam clearance was significantly lower in HIV-infected patient compared with healthy volunteers (CI95% = 0.68–0.92) and a significant relationship was found with TNF-α (r = −0.66, p = 0.008) | Imai et al. (2011) |
| | | | - urinary dextromethorphan MR was significantly higher in HIV-infected patients than in healthy volunteers (CI95% = 2.36–42.48) and a trend was observed for an association with the increase in TNF-α concentration (r = 0.49, p = 0.06) | Case-control study |
| | | | - caffeine metabolism was not significantly different in HIV-infected subjects compared to non-smokers healthy volunteers (controlled for smoking status) (CI95% = 0.83–3.11) | Gatti et al. (1993) |
| | | | | |
| HIV-infected patients vs control | midazolam (CYP3A) and dextromethorphan (CYP2D6) | 30 = HIV-infected | - CYP3A4 activity in HIV infected patients was approximately 50% of the activity in healthy volunteers but it was mainly attributable to a lower intestinal CYP3A4 activity, while hepatic CYP3A was not different | Case-control study |
| | | | - CYP2D6 activity was essentially comparable | Jones et al. (2010) |
| | | 12 = healthy volunteers | | |
| HIV-positive patients | dextromethorphan (CYP2D6) | 61 | - 2 of the 59 patients with an NM genotype expressed a PM phenotype and 4 NM genotype patients were less extensive dextromethorphan metabolizers than any of the patients receiving medication known to inhibit CYP2D6 | | |
| HIV-1 infected patients vs control | darunavir (CYP3A) | Unknown, information obtained from Summary of Product Characteristics (SmPC) | - exposure to darunavir was higher in HIV-1 infected patients | Cohort study |
| | | | - explained by the higher concentrations of α1-glycoprotein in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations | Case-control study |
| | | | | |
| HIV-infected patients vs healthy volunteers | saquinavir (CYP3A) | 33 = HIV-infected | - co-administration of ketoconazole increased saquinavir AUC by 190 and 69% in healthy volunteers and HIV-infected patients, respectively while co-administration of rifampicin decreased saquinavir area under the curve by 70 and 46% | European medicines agency |
| | | | | |
| HIV-infected patients vs healthy controls | atazanavir and atazanavir with ritonavir (CYP3A) | 12 and 14 = control | - mean AUC of atazanavir and atazanavir with ritonavir were 29’303 and 61’435 ng*h/mL respectively in healthy volunteers, vs. 22’262 and 53’761 ng*h/mL, respectively in HIV-infected patients | Grub et al. (2001) |
| | | | | |
| HIV-infected patients vs healthy controls | lopinavir with ritonavir (CYP3A) | Unknown, information obtained from SmPC | - no substantial differences observed between the two groups | Packageinserts |
| | | | | |
| | | | | |

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Marzolini et al., 2020; Schoergenhofer et al., 2020; Testa et al., 2020). Indeed, the plasma concentrations of some CYP3A substrates (lopinavir, darunavir and direct oral anticoagulants) were significantly increased in patients with SARS-CoV-2 infection (Cojutti et al., 2020; Gregoire et al., 2020; Schoergenhofer et al., 2020; Testa et al., 2020). CRP and IL-6 were also associated with lopinavir concentrations and a trend toward a return to baseline was observed after treatment with tocilizumab (Marzolini et al., 2020; Schoergenhofer et al., 2020). Indeed, lopinavir through level in patients with SARS-CoV-2 infection was twice as high as in HIV patients but concentrations decreased when tocilizumab was administered (Marzolini et al., 2020; Schoergenhofer et al., 2020). However, the impact of inflammation induced by SARS-CoV-2 infection on lopinavir through concentration may be also due to increased orosomucoid levels (Boffito et al., 2021; Stanke-Labesque et al., 2021). Lopinavir is a highly protein-bound drug and the misinterpretation of its overexposure during inflammation could be explained by the fact that total and not unbound concentration was considered (Boffito et al., 2021; Stanke-Labesque et al., 2021). Furthermore, a case report described clozapine toxicity and increased clozapine level from 0.57 to 0.73 mg/L during SARS-CoV-2 infection (Cranshaw et al., 2021; Stanke-Labesque et al., 2021). Moreover, the occurrence of bleeding events a few days after vaccination, when the PT time was previously stable, has been described (Kramer, 1984; Weibert et al., 1986; Carroll and Carroll, 2009). Indeed, the plasma concentrations of some CYP3A substrates (lopinavir, darunavir and direct oral anticoagulants) were significantly increased in patients with SARS-CoV-2 infection (Cojutti et al., 2020; Gregoire et al., 2020; Schoergenhofer et al., 2020; Testa et al., 2020). Indeed, the plasma concentrations of some CYP3A substrates (lopinavir, darunavir and direct oral anticoagulants) were significantly increased in patients with SARS-CoV-2 infection (Cojutti et al., 2020; Gregoire et al., 2020; Schoergenhofer et al., 2020; Testa et al., 2020). Indeed, the plasma concentrations of some CYP3A substrates (lopinavir, darunavir and direct oral anticoagulants) were significantly increased in patients with SARS-CoV-2 infection (Cojutti et al., 2020; Gregoire et al., 2020; Schoergenhofer et al., 2020; Testa et al., 2020). Indeed, the plasma concentrations of some CYP3A substrates (lopinavir, darunavir and direct oral anticoagulants) were significantly increased in patients with SARS-CoV-2 infection (Cojutti et al., 2020; Gregoire et al., 2020; Schoergenhofer et al., 2020; Testa et al., 2020).

### Vaccination

Regarding vaccination (Table 3), several reports and studies assessed variations of PK/PD parameters of drugs after vaccination, but data remain contradictory. Of the 31 articles included, 28 were exclusively about influenza vaccination while two were about concomitant vaccinations including influenza (pneumococcus, tetanus and hepatitis A). Only one article did not evaluate the influenza vaccination but reported on the impact of tuberculosis vaccination (BCG). No significant difference of CYP activity between before or after vaccination was shown in several studies (Britton and Ruben, 1982; Fischer et al., 1982; Goldstein et al., 1982; Patriarca et al., 1983; Stults and Hashisaki, 1983; Stults and Hashisaki, 1983; Hayney and Muller, 2003). In particular, the impact of vaccination on anticoagulants effects has been well-studied but the majority of studies showed no variation of PT time or INR (Farrow and Nicholson, 1984; Kramer et al., 1984; Gomolin, 1986; Raj et al., 1995; Poli et al., 2002; Palliani et al., 2003; Iorio et al., 2006; Jackson et al., 2007; MacCallum et al., 2007; Casajuana et al., 2008). However, the occurrence of bleeding events a few days after vaccination, when the PT time was previously stable, has been described (Kramer et al., 1984; Weibert et al., 1986; Carroll and Carroll, 2009). Moreover, the case of a patient hospitalized because of serum CPK level of 93,000 U/L during treatment with cerivastatin and bezafibrate or the occurrence of tramadol toxicity has been reported (Plotkin et al., 2000; Pellegrino et al., 2013). The patient had been vaccinated 5 days earlier (Plotkin et al., 2000). Other studies, few in number, have found an effect of vaccination on the PK of CYP substrates (Revent et al., 1980; Kramer and McClain, 1981; Gray et al., 1983). However, no study has correlated the data with pro-inflammatory markers.

### Organs Diseases

The influence of liver and kidney function on disposition of drugs excreted by the liver and kidney is widely recognized and used to derive dosing adaptations. However, there is now an increasing appreciation that kidney impairment can also reduce non-renal clearance and alter the bioavailability of drugs predominantly metabolized by the liver (Nolin, 2008). Indeed, uremic toxin has been implicated in transcriptional, translational and acute posttranslational modifications of CYP, and it has been recognized that inflammation is a common feature in end-stage renal disease (ESRD) patients (Nolin, 2008; Stenvinkel and Alvestrand, 2002). For example, CYP3A activity increased post-dialysis, meaning that it is the presence of uremic toxin that is responsible for CYP downregulation and not the underlying disease (Nolin et al., 2006). An inverse relationship between hepatic CYP3A activity was found in this study, but it did not prove causality (Nolin et al., 2006). It indicates that uremia can be used as a surrogate for dialyzable toxins that contribute to

### Table 3C | Continued Impact of HIV on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|--------------------|-------------------------------|-----------------------|
| HIV-infected patients vs healthy controls | atazanavir (CYP3A) | 10 = HIV-infected | - mean atazanavir AUC in HIV-infected patients was 14’187 ng*h/ml compared with 33’087 ng*h/ml in healthy volunteers | Le Tiec et al. (2005) |
|                                |                               | 36 = healthy volunteers | - after 14 and 20 days of atazanavir in HIV patients and healthy volunteers, AUC were 46’073 and 57’039 ng*h/ml | Case-control study |
| Patients with different stage of HIV infection vs control | caffeine (CYP1A2) | 29 = AIDS | - metabolic status was not change in HIV asymptomatic patients but changed in AIDS patients (with acute illnesses or stable) | Venuto et al. (2018) |
|                                |                               | 29 = AIDS-stable |                               | Case-control study |
|                                 | atazanavir (CYP3A) | 18 = HIV-infected | - apparent oral clearance was not significantly correlated with inflammatory biomarkers | Lee et al. (1993) |
|                                |                               | 29 = control |                               | Cohort study |
| HIV infected patients | atazanavir (CYP3A) | 107 = HIV-1 infected |                               |                       |
alterations in CYP3A function (Nolin et al., 2006). Indeed, hemodialysis improved CYP3A activity with a 27% increase 2 h post-dialysis in uremic patients, suggesting that potential toxins responsible for this alteration were removed (Nolin et al., 2006). Authors suggested that this improvement occurred independently of transcriptional or translational modifications, contrary to what has been suggested previously (Nolin et al., 2006). However, as shown in Table 4, two studies found an association between the modification of CYP activity and inflammation in ESRD patients (Molanaei et al., 2012; Molanaei et al., 2018).

All studies in patients with liver disease described a decrease in CYP activity, compared to controls, as shown in Table 5. Indeed, several studies conducted antipyrine, an old drug that is metabolized by multiple CYP (Branch et al., 1973; Farrell et al., 1979; Salmela et al., 1980; Teunissen et al., 1984; Schellens et al., 1989; Bauer et al., 1994; Gricco et al., 1998; Frye et al., 2006). They showed that CYP activity and antipyrine metabolism decreased only in severe disease compared to inactive cirrhosis, mild-moderate liver disease or healthy volunteers (Farrell et al., 1979; Bauer et al., 1994; Gricco et al., 1998). Moreover, chronic liver disease appeared to have a higher impact than an acute/reversible pathology (Branch et al., 1973). However, few studies have focused on a specific CYP substrate, and no studies found an association with inflammatory markers. One study demonstrated that CYP2C19, 2E1, 1A2 and 2D6 probe drugs concentrations were inversely correlated to the Child-Pugh score and another one demonstrated that phenacetin clearance decreased by 90% in patients with cirrhosis (Frye et al., 2006; Wang et al., 2010). Concerning CYP2C9, tolbutamide plasma levels increased by 10–20% and irbesartan AUC increased by 20–30% in cirrhotic patients (Ueda et al., 1963; Marino et al., 1998). The same results were found with CYP3A as diazepam clearance decreased in cirrhosis (Klotz et al., 1975). These variations may therefore be attributed to the loss of liver function due to tissue destruction. CYP metabolism appeared to be influenced by other organ’s disease, such as clozapine serum levels that increased by 2-fold during chronic obstructive pulmonary disease (COPD) exacerbation and antipyrine clearance that was significantly lower in patient with COPD and antitrypsin deficiency than in healthy volunteers (Laybourn et al., 1986; Leung et al., 2014). In addition, one study showed that inflammatory markers were inversely correlated with CYP1A2 and CYP2C19 activity but not with CYP2D6 and CYP2E1 activity in patients with congestive heart failure (Frye et al., 2002).

Some studies conducted in critically ill patients (Table 8), showed that CYP1A2 and 3A metabolic activity were downregulated, and that it may be proportional to the severity and reversibility of the illness (Shelly et al., 1987; Toft et al., 1991; Kruger et al., 2009). For instance, theophylline clearance decreased by 10–66%, atorvastatin AUC increased by 15-fold, and clopidogrel active metabolite decreased by 48-fold, raising concerns about

### Table 2D | Impact of SARS-CoV-2 on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction |
|--------------------------------|-------------------------------|--------------------|--------------------------------|
| SARS-CoV-2 and treatment with tocolizumab | lopinavir/ritonavir (CYP3A) and hydroxychloroquine (CYP2D6) | 41 without tocilizumab, 51 = tocilizumab (35 before and 16 after) | lopinavir concentrations positively correlated with CRP (r = 0.37, p < 0.001) and significantly lower after tocilizumab, no correlation between CRP and hydroxychloroquine plasma concentration |
| SARS-CoV-2 vs. HIV-patients | lopinavir/ritonavir (CYP3A) | 12 | lopinavir trough concentration in patients with SARS-CoV-2 infection were significantly higher than those usually observe in HIV-infected patients (18,000 vs. 5,965 ng/ml) |
| SARS-CoV-2 | clozapine (CYP1A2) | 38-year-old-man | - symptoms of clozapine toxicity, - clozapine level increased by 0.57–0.73 mg/L and norclozapine increased by 0.22 mg/L to 0.31 mg/L after SARS-CoV-2 infection |
| SARS-CoV-2 | lopinavir/ritonavir (CYP3A) | 8 | - through concentration associated with CRP level (r = 0.81, p = unknown), - trough levels were 2-fold higher in patients with SARS-CoV-2 infection than HIV patients |
| SARS-CoV-2 | apixaban (CYP3A), rivaroxaban (CYP3A), edoxaban (CYP3A) | 5 = apixaban, 3 = rivaroxaban, 3 = edoxaban | - alarming increase in DOAC plasma levels compared to pre-hospitalization levels, - possible role of concomitant drugs (CYP3A inhibitors) or disease-related organ dysfunctions |
| SARS-CoV-2 vs HIV-patients | darunavir (CYP3A) | 30 = SARS-CoV-2, 25 = HIV | - median CL/F was significantly lower in SARS-CoV-2 patients with IL-6 levels >18 pg/ml than <18 pg/ml or HIV patients (p < 0.0001), - increasing level of IL-6 affected concentration vs time simulated profile |
TABLE 3 | Impact of vaccination on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|------------------------------|--------------------|--------------------------------|-----------------------|
| **Influenza vaccination**     | Erythromycin breath-tests (ERMBT) (CYP3A) | 24 = healthy volunteers | - no significant difference between CYP3A4 activity before and 7 days after vaccination but the influenza antigen-specific production of IFN-γ by lymphocytes was highly correlated with the change in ERMBT (r = -0.614, p = 0.020) thus, IFN-γ downregulates the expression/activity of CYP3A4 | Boffito et al. (2021) |
|                               | ERMBT (CYP3A)                 | 15 = healthy volunteers | - significant inverse correlation between age and change in ERMBT (r = -0.624, p < 0.015) after vaccination | Non-random |
|                               | Simvastatine (CYP3A)         | 68-year-old man       | - hospitalized because of complaining of extreme weakness and diffuse muscle pain 5 days after influenza vaccine | Case report |
|                               | Chloroxazone (CYP2E1)        | 10 = healthy volunteers | - no significant difference in the PK parameters before immunization and 7 and 21 days after vaccination | Stults and Hashisaki (1983) |
| **Influenza vaccination vs controls** | 13C-aminopyrine breath test (CYP2C19, 1A2 and 3A4) | 12 = vaccinated | - significant reduction (22–74%, p < 0.001) in aminopyrine breath test 7 days after vaccination compared to controls | Fischer et al. (1982) |
|                               |                              | 10 = controls         | - metabolic activity depression was not significant 2 days after vaccination but there was still a significant reduction 21 days after vaccination | Non-random |
| **BCG vaccination**           | Theophylline (CYP1A2)        | 9 = patients converted to positive Mantoux skin test | - the clearance and half-life were significantly decreased and increased, respectively (p < 0.02), in patients with positive Mantoux skin test, as compared to controls | Stults and Hashisaki (1983) |
| **Influenza vaccination**     | Theophylline (CYP1A2)        | 3 = controls          | - plasmatic concentration before and after influenza vaccination significantly increased | Random |
|                               |                              | 7–3 recovering from an acute exacerbation of COPD and 4 healthy volunteers | | Goldstein et al. (1982) |
| **Influenza vaccination**     | Theophylline (CYP1A2)        | 13                  | - no difference in the mean serum theophylline levels before influenza vaccination and 24h, 72h, 1 week and 2 weeks after vaccination | Non-random |
|                               |                              | 7 (chronic bronchitis and chronic airflow obstruction thus and 5 men were smokers (CYP1A2 inductor)) | - no difference between the clearance rate before and 24 h after vaccination (p = 0.778) | Patriarca et al. (1983) |
|                               |                              | 16 (COPD)            | - no difference in plasma concentration 24 h before or after vaccine injection | Non-random |

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| Inflammation characterized by | Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-----------------------------|--------------------|--------------------------------|-----------------------|
| Influenza vaccination         | theophylline (CYP1A2)       | 5                  | - no significant variations in the serum levels before and 24 h after vaccination | Farrow and Nicholson (1984), Non-random |
| Influenza vaccination         | theophylline (CYP1A2) and chlordiazepoxide (CYP3A) | 8 = theophylline, 5 = chlordiazepoxide | - an effect of vaccination has been shown on theophylline clearance at day 1 after vaccination \( (p = 0.016) \) but not at day 7 \( (p = 0.314) \) | MacCallum et al. (2007), Non-random |
| Influenza vaccination vs controls | theophylline (CYP1A2) and warfarin (CYP2C9) | 152 = influenza vaccinated, 51 = unvaccinated | - no effect on chlordiazepoxide metabolism - the effect seems to be greater when initial clearance is higher - no ADR occurred in patients on theophylline in both groups and only one reaction in each group of patients who were taking warfarin | Raj et al. (1995), Case-control study |
| Influenza, pneumococcal, tetanus and hepatitis A vaccinations | warfarin (CYP2C9) | 51 = unvaccinated, 5167 = placebo | - not associated with INR value change | Gomolin (1986), Cohort study |
| Influenza and pneumococcal vaccination vs. controls | warfarin (CYP2C9) | 25 = placebo, 25 = influenza, 19 = pneumococcal | - no statistically significant increments in mean British Corrected Ratios for prothrombin time 2, 7- or 21-days post injections | Iorio et al. (2006), Random |
| Influenza vaccination         | warfarin (CYP2C9) | 78 = vaccinated, 72 = controls | - no significant effect on anticoagulant control during the 10 days post-vaccination in the vast majority of individuals | Poli et al. (2002), Case-control study |
| Influenza vaccination         | warfarin (CYP2C9) | 41 = placebo, 41 = influenza | - no significant difference in the mean PT 3, 7 and 14 days after vaccination for the entire group and no patient developed any major or minor bleeding episodes | Palani et al. (2003), Case-control study |
| Influenza vaccination vs controls | warfarin (CYP2C9) | 7 = placebo, 7 = influenza | - no difference in the mean PT one, three and 6 weeks after vaccination | Casajuana et al. (2008), Case-control study |
| Influenza vaccination         | warfarin (CYP2C9) | 104 = placebo, 104 = influenza | - no difference in the mean PT-INR values and mean weekly dosage between group 1 (active vaccine at day 0 and placebo at day 42) and group 2 (placebo at day 0 and active vaccine at day 42) | Kramer et al. (1984), Cross-over study |
| Influenza vaccination         | warfarin (CYP2C9) | 71 = vaccinated, 72 = controls | - no differences in the anticoagulation levels 3 months before and 3 months after the vaccination, - in the 34 vaccinated patients older than 70 years, a reduction of anticoagulation intensity was achieved in the 3 months after the vaccination and it was not the case in control group | Carroll and Carroll (2009), Case-control study |
| Influenza vaccination         | warfarin (CYP2C9) | 49 = patients, 45 = controls | - no difference in INR between patients and control groups before vaccination while 7–10 days after injection, INR significantly increased \( (p < 0.00005) \), - in patient group, INR increased significantly after vaccination \( (p < 0.00001) \) | Weibert et al. (1986), Case-control study |

(Continued on following page)
treatment efficacy (Toft et al., 1991; Kruger et al., 2009; Schoergenhofer et al., 2018). However, a systematic review reported that 20–65% of critically patients had an increased renal clearance, defined as a creatinine clearance greater than 130 ml/min/1.73 m² (Bilbao-Meseguer et al., 2018). This underscores the fact that inflammation has a different effect on drug clearance through the different mechanisms of drug elimination.

### Diabetes

In diabetes (Table 9), CYP metabolism has been shown to be downregulated (Salmela et al., 1980; Pirttiaho et al., 1984).

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**Table 3** (Continued) Impact of vaccination on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction | References and design |
|------------------------------|------------------------------|--------------------|--------------------------------|-----------------------|
| Influenza vaccination        | 22S acenocoumarol 4 warfarin (CYP2C9) | 100 = intramuscular, 129 = subcutaneous | - INR decreased 24 h after intramuscular vaccination and increased in the subcutaneous group but the difference did not reach statistical significance | Plotkin et al. (2000), RCT |
| Influenza vaccination        | warfarin (CYP2C9) | 8 | 40% prolongation of PT (statistically significant unknown) | Pellegrino et al. (2013), Non-random |
| Influenza vaccination        | warfarin (CYP2C9) | 12 (healthy volunteers) | - no significant effect on warfarin metabolism was observed between influenza vaccination or saline injection | Pellegrino et al. (2013), Cross-over study |
| Influenza vaccination        | warfarin (CYP2C9) | 81-years-old man | - admitted with hematemesis and a 3-days history of melena and further investigations confirmed a bleeding gastric mucosa but no evidence of oesophagitis, gastritis, duodenitis or ulcer, - monthly PT had been stable and in the therapeutic ranges but the day of admission, PT was 36 s, - 10 days before admission, he received influenza vaccination. Warfarin was withheld and recovered uneventful | Kramer and McClain (1981), Case report |
| Influenza vaccination        | warfarin (CYP2C9) | 64-years-old patient | - death from intracranial haemorrhage (INR = 15 at admission), - INR = 2.45 weeks before and all values over the previous 6 months were relatively stable, - vaccine 4.5 weeks before this fatal event | Gray et al. (1983), Non-random |
| Influenza vaccination        | warfarin (CYP2C9) | 12 | - small but significant increase in the PT ratio before and after vaccination, - maximal increase occurred on day 14 and represented a 7.6% increase over the baseline value | Renton et al. (1980), Case report |
| Influenza vaccination        | tramadol (CYP2B6 and 3A, bioactivated by CYP2D6) | 85-years-old woman and a and 84-years-old man | - hallucinations and other neurologic symptoms six and 5 days after the administration of two different influenza vaccines | Nolin (2008), Case report |
| Influenza vaccination        | carbamazepine (CYP1A2 and 2C9, bioactivated by CYP3A) | 15-years-old woman | - vaccination 13 days before admission, but it was well tolerated, and no changes were made in her medication, - serum carbamazepine level was 27.5 μg/ml (ataxia and increasing lethargy) at admission and it decreased to 9.1 μg/ml 4 days after admission | Nolin et al. (2008), Random |
| Influenza vaccination        | phenytoin (CYP2C9 and CYP2C19 substrates and induces CYP2C9, 2C19 and 3A) | 16 | - no significant increase in mean serum concentration were observed on days 7 and 14 following the vaccination, - temporary increases of 46–170% mean serum concentration occurred in four subjects | Stenvinkel and Alvestrand (2002), Cohort study |
| Influenza vaccination        | acetaminophen (CYP2E1), alprazolam (CYP3A), antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 24 (healthy volunteers 9 = acetaminophen, 7 = alprazolam, 8 = antipyrine) | - PK variables were no significantly different (p > 0.05) before and 7 and 21 days after vaccination | Nolin et al. (2006), Random |
TABLE 4 | Impact of renal diseases on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-----------------------------|-------------------|-------------------------------|-----------------------|
| Severe impairment of renal function vs normal | tolbutamide (CYP2C9), alprazolam (CYP3A4) | 11 severe kidney impairment, 7 normal | - Half-life was prolonged in severely impaired renal function patients (in renal impairment = 1.1) | Molanaei et al. (2018), Case-control study |
| Haemodialyzed patients | | 26 | - Ratio of unconjugated alprazolam to 4-hydroxyalprazolam was correlated with CRP levels (r = 0.49, p < 0.01), compared to controls. | Molanaei et al. (2012), Cohort study |

### Haemodialyzed patients

| Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction |
|-----------------------------|-------------------|-------------------------------|
| quinine (CYP3A4) | 44 | - Significant correlation between the ratio of quinine/3-OH-quinine and median CRP (r = 0.48, p = 0.001), ocosomucoid (r = 0.44, p = 0.003) and IL-6 after 12 h drug intake (r = 0.43, p = 0.004), correlation is no longer significant for IL-6 and ocosomucoid after adjustment for age, gender, diabetes mellitus, d Yatesis, PTH, ocosomucoid and medications and it remains borderline for CRP (r = 0.05) |

### End stage renal disease (ESRD) vs control

| Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction |
|-------------------------------|-------------------|-------------------------------|
| warfarin (CYP2C9) | 7 = ESRD | - 50% (p < 0.05) increase plasma warfarin S/R ratio relative to controls |
| 6 = control | | |
| Moderate and severe kidney impairment vs no/mild kidney impairment | | - 50% (p < 0.05) increase plasma warfarin S/R ratio relative to controls |
| warfarin (CYP2C9) | 599 = no/mild | - Patients with moderate kidney impairment required 9.5% lower doses (p < 0.001) compared to controls. - Patients with severe kidney impairment required 19.1% lower doses (p < 0.001) compared to controls. - Reduced kidney function was associated with lower dose requirements independently of CYP2C9 and VKORC1 genotype and clinical factors |
| 300 = moderate | | |
| 61 = severe | | |

**References and design**

- Molanaei et al. (2018), Case-control study
- Molanaei et al. (2012), Cohort study
- Farrel et al. (1979), Cohort study
- Frye et al. (2009), Case-control study
- Grieco et al. (1998), Two cohort studies combined, Case-control study
### TABLE 5 | Impact of liver diseases on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYP concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|------------------------------|-------------------|--------------------------------|-----------------------|
| Mild to moderate hepatocellular changes or inactive cirrhosis and severe liver disease vs control | antipyrene (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 15 = mild-moderate hepatocellular damage, 13 = inactive cirrhosis, 22 = severe liver disease, 21 = controls | - mean value of hepatic CYP concentration did not differ between patients with mild to moderate hepatocellular changes (less than 50% hepatocytes morphologically abnormal) or inactive cirrhosis and controls and antipyrine half-life did not significantly differ between all groups. - CYP concentration was less in patients with severe liver disease (more than 50% hepatocytes morphologically abnormal or active cirrhosis) and, thus, antipyrine half-life was significantly lower (p < 0.01) compared to other groups | Bauer et al. (1994), Case-control study |
| Liver disease vs. control | caffeine (CYP1A2), mephenytoin (2C19), debrisoquin (2D6), and chloroxzone (2E1) | 20 = liver disease | - significant decrease in metabolite production in patients with liver disease for CYP2C19 (p < 0.001), 2E1 (p = 0.0081), 1A2 (p = 0.0054) and 2D6 (p = 0.0110) | Salmela et al. (1993) Case-control study |
| Chronic active hepatitis and cirrhosis vs. control | antipyrene (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 103 = controls, 101 = non-cirrhotic with liver metastases, 102 = chronic active hepatitis, 92 = confirmed cirrhosis, 120 = hepatocellular carcinoma and cirrhosis | - clearance was significantly impaired with respect to healthy volunteers, chronic hepatitis without fibrosis and non-cirrhotic patients with liver metastases. - mean clearance rate of the non-cirrhotic patients with liver metastasis was quite similar to that of patients with healthy livers. - cirrhotic patients with hepatocellular carcinoma also presented significantly impaired clearance compared with that of healthy volunteers and patients with liver metastasis. - elimination of antipyrene may very well be normal in patients with primary or metastatic liver disease, even when there is extensive tumour involvement | Branch et al. (1973), Case-control study |
| Cirrhotic patient and chronic hepatitis vs. control | antipyrene (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 6 = control, 6 = chronic active hepatitis, 5 = cirrhosis | - half-life and clearance were significantly higher and lower respectively in cirrhotic patients compared with healthy subjects. - no significant differences between hepatitis patients and healthy subjects | Schelfens et al. (1989), Case-control study |
| Diabetics with fatty liver, fatty liver with inflammatory changes and with cirrhosis vs diabetics with normal liver | antipyrene (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 4 = control, 13 = fatty liver, 33 = fatty liver with inflammation, 6 = cirrhosis | - clearances decreased significantly in diabetics with fatty liver (p = 0.005), in diabetics with fatty liver with inflammatory changes (n = 33, p < 0.005) and in diabetics with cirrhosis (n = 6, p < 0.005) as compared to diabetics with normal liver - disappearance rate was reduced in five of ten cases, - half-life was prolonged to 7.8–11.2 h (4.4 h in normal group), - plasma levels after 24 h were 11.4–20.8% of the theoretical initial value (5.3% of the theoretical initial value in normal group) | Teunissen et al. (1984), Case-control study |
| Cirrhosis vs. normal | tolbutamide (2C9) | 10 = cirrhotic patients, 7 = normal | - half-life and clearance were significantly reduced in cirrhotic patients compared with healthy controls | Molanaei et al. (2018) Case-control study |
| Acute liver and chronic disease | antipyrene (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 14 = control, 38 = liver disease | - half-life was prolonged in patients with liver disease and those with chronic illness had greater increase than those with acute, reversible pathology | Wang et al. (2010), Case-control study |
| Various liver disease vs. controls | antipyrene (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4), theophylline (CYP1A2) | 24 = liver disease, 26 = controls | - clearance of antipyrene, hexobarbital and theophylline are lower than those found in the control subject | Liver disease = Ueda et al. (1963) , Controls = Marino et al. (1998), Case Control |
| Alcoholic cirrhosis vs. controls | antipyrene (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 23 = alcoholic liver cirrhosis, 17 = control | - clearance was significantly lower in patients with alcoholic cirrhosis as compared with healthy volunteers (p < 0.001), - the rates antipyrene formations metabolites were not reduced to the same extent | Klotz et al. (1975) Case-control study |
| Chronic hepatitis | mephenytoin (CYP2C9 and 2C19 and induces 2C9, 2C19 and 3 A) | 35 = chronic hepatitis, 153 = controls | - mean metabolite excretion was significantly lower in patients with liver disease (p < 0.005) | Laybourn et al. (1986), Case-control study |

(Continued on following page)
Indeed, antipyrine metabolism was decreased compared with controls in several studies (Salmela et al., 1980; Pirttiaho et al., 1984; Zysset and Wietholtz, 1988). One study using a cocktail approach showed that CYP2B6, CYP2C19 and CYP3A activity decreased, CYP1A2 and CYP2C9 activity increased, and CYP2D6 and CYP2E1 activity was unaffected in type II diabetes (T2D) (Gravel et al., 2019). However, conflicting results exist with tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988). Regarding CYP3A, one study found no impact on amlodipine or tolbutamide and paracetamol half-lives which were unchanged and increased respectively (Ueda et al., 1963; Adithan et al., 1988).
TABLE 6 | Impact of lung diseases on CYP activities.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|--------------------------------|--------------------|--------------------------------|-----------------------|
| COPD exacerbation             | clozapine (CYP1A2)             | 52-year-old woman  | - symptoms of clozapine toxicity, - serum levels = 1400 ng/ml (References = 350–700 ng/ml) | Luong et al. (2016), Case reports |
| Chronic obstructive lung (COLD) and pulmonary disease caused by α1-antitrypsin (AAT) deficiency vs. control | antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 35 = AAT, 25 = COLD, 31 = control | - clearance was not different in AAT and COLD patients (p > 0.2), - clearance significantly higher in healthy volunteers than in patients with COLD (18%, p < 0.01) | Bilbao-Meseguer et al. (2018), Case-control study |

TABLE 7 | Impact of cardiac diseases on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|--------------------------------|--------------------|--------------------------------|-----------------------|
| Congestive heart failure      | caffeine (CYP1A2), mephenytoin (2C19), dextromethorphan (2D6), chloroxazone (2E1) | 16 | - IL-6 levels were inversely correlated to CYP1A2 (r = -0.56, p = 0.0235) and CYP2C19 (r = -0.63, p = 0.0084) activities, - TNF-α was inversely correlated to CYP2C19 (r = -0.61, p = 0.0118) activity, - no significant relationship between IL-6 and TNF-α with CYP2D6 and 2E1 activities | Pirttiaho et al. (1984), Cohort study |

cytokines. Indeed, it is well-established that chronic inflammation is involved in the pathophysiology of diabetes and the more complex condition of metabolic syndrome (Gravel et al., 2019). TNF-α can lead to the development of diabetes by affecting insulin action, and levels of inflammatory cytokines and markers are reported to be increased in diabetes patients (Darakjian et al., 2021). In a multivariate analysis, IFN-γ, IL-1β, IL-6 and TNF-α were associated with CYP activities, depending on the CYP isoenzyme (Gravel et al., 2019). However, type I (T1D) and type II diabetes did not appear to have the same impact on CYP metabolism (Dyer et al., 1994; Korrapati et al., 1995; Lucas et al., 1998; Zysset and Wietholtz, 1988; Matzke et al., 2000; Rotaniemi et al., 2002; Wang et al., 2003). The impact of inflammation may be different partly because of obesity, which is more common in T2D (Wang et al., 2003). Indeed, obese patients had a 40% increase in CYP2E1 activity (Lucas et al., 1998; Wang et al., 2003). CYP2E1 increased activity could also be attributed to hypo-insulinemia, as administration of insulin reverses this induction at the mRNA level (Lucas et al., 1998). Moreover, moderate controlled T1D had comparable CYP2E1 activity to healthy volunteers (Wang et al., 2003). This was confirmed in other studies that showed an unaffected metabolic clearance rate of antipyrine in well-controlled (by insulin) T1D (Zysset and Wietholtz, 1988; Rotaniemi et al., 2002). This could also be explained by insulin supplementation and the subsequent correction of ketones that leads to a return to baseline level for CYP2E1 expression (Wang et al., 2003). Indeed, ketones have been shown to be an important modulator of CYP2E1 by enhancing its protein expression and mRNA level (Wang et al., 2003). This has been confirmed with CYP1A2, where fluctuations in growth hormone levels, hyperketonemia and variation in glucose metabolic steady state and HbA1C levels may contribute to these changes (Bechtel et al., 1988; Korrapati et al., 1995; Matzke et al., 2000). The difference in classification criteria for T1D and type 2 diabetes may explain the inconsistent findings (Matzke et al., 2000). Further studies to discriminate between these two entities are needed (Zysset and Wietholtz, 1988).

Overall, CYP3A, 2C19 and 2B6 activity appear to be downregulated while CYP1A2 activity was increased and CYP2D6 activity was unchanged in diabetic patients (Bechtel et al., 1988; Urry et al., 2016; Gravel et al., 2019). Conflicting results remain regarding CYP2C9 and CYP2E1 (Ueda et al., 1963; Adithan et al., 1988; Lucas et al., 1998; Gravel et al., 2019).

Auto-Immune Diseases

Few studies observed the impact of auto-immune disease on CYP activities, such as psoriasis, systemic lupus erythematosus (SLE), Behçet's disease, rheumatoid arthritis (RA), Crohn's disease and celiac disease (Table 10). In contrast to what has been observed for CYP2D6 in other inflammatory states, two studies observed CYP2D6 downregulation in patient with SLE (Idle et al., 1978; Baer et al., 1986). However, these studies have some limitations, such as the presence of concomitant medications inhibiting the metabolism of CYP2D6 and the absence of adequate randomization (Baer et al., 1986). Even though RA is one of the most prevalent chronic inflammatory disease, only two case-control studies were found in the literature studying the impact of
RA on the PK and PD of verapamil and losartan, respectively (Mayo et al., 2000; Daneshtalab et al., 2006; Smolen et al., 2016). Verapamil is metabolized by CYP3A and 1A2 into norverapamil (Tracy et al., 1999). Verapamil and norverapamil metabolism has been shown to be reduced in patients with RA compared to healthy volunteers (Mayo et al., 2000). Verapamil was not more dromotropic or hypotensive in RA patients (Mayo et al., 2000). Inhibition of CYP2C9 was proportional to RA disease severity in another study, but this was not accompanied by reduced clinical response after losartan administration (Daneshtalab et al., 2006).

Same results were found in patients with Behcet’s disease. Indeed, one study observed downregulation of CYP2C9 in Behcet’s patients (Goktaş et al., 2015). However, losartan’s MR in nine patients with Behçet’s disease taking colchicine were similar to those not taking colchicine (Goktaş et al., 2015). This may be because the drug had been taken for only 2 weeks (Goktaş et al., 2015).

In Crohn’s disease, S-verapamil concentration was higher than R-verapamil while the opposite was found in normal conditions and higher plasma levels of propranolol were

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-----------------------------|--------------------------------|--------------------|---------------------------------|----------------------|
| Septicaemia with shock and respiratory failure and multiple organ dysfunction | theophylline (CYP1A2) and ethylene-diamine (CYP3A) | 6 | - 10-66% reduction of theophylline clearance as compared to healthy volunteers. Half-life was 18.6 h compared to a normal value of 6 h, - 54% reduction of ethylenediamine clearance and half-life was 2.3 h, which is 5 times the normal value of 0.55 h | Zysset and Wietholtz (1988), Cohort study |
| Critically ill patients (ICU) with sepsis vs control | atorvastatin (CYP3A) | 12 = ICU with sepsis, 5 = healthy volunteers | - 18-fold higher Cmax (p < 0.001) and 15-fold higher AUC (p < 0.01) | Gravel et al. (2019), Case-control study |
| Critically ill patients | midazolam (CYP3A) | 6 | - CYP3A downregulation is proportional to the severity of the patient’s illness and reversible, - normal values from other studies | Preston et al. (2001), Case-control study |
| Multiply injured patients vs. healthy volunteers | mephénytoïn (CYP2C19), chlorzoxazone (CYP2E1), dapsone (multiple CYP) and flurbiprofen (CYP2C9) | 23 = multiple injured patients, 90 = control | - CYP2C19 and 2E1 activity significantly reduced in trauma patients as compared to healthy volunteers, - CYP2C9 and multiple CYP activities (dapsone) higher after injury as compared to healthy volunteers, - CYP2C19 and 2E1 activities correlated with MODS and MOF scores | Marques et al. (2002), Case-control study |
| Critically ill patients | clopidogrel (bioactivated by CYP2C19), pantoprazole (CYP2C19) | 43 = clopidogrel, 16 = pantoprazole | - CYP2C19 and 2E1 activity significantly reduced in trauma patients as compared to healthy volunteers, - CYP2C9 and multiple CYP activities (dapsone) higher after injury as compared to healthy volunteers, - median ratio of clopidogrel active metabolite to clopidogrel concentration was 0.6 and this ratio was 48-fold higher (p < 0.001) in healthy volunteers, - 70% of critically ill patients were insufficiently treated with clopidogrel, - 5-fold increased pantoprazole half-life | Akhlaghi et al. (2012), Cohort study |
### Table 9: Impact of diabetes on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|-------------------|-------------------------------|-----------------------|
| Non-insulin dependent (NDI) diabetic subjects with fatty liver vs. healthy subjects | antipyrine (CYP1A2), 2B6, 2C8, 2C9, 2C18 and 3A4 | 21 = diabetes, 11 = control | - NID diabetic subjects with fatty liver have lowered hepatic drug metabolism enzyme capacity as assessed per unit weight of liver tissue compared with healthy subjects (p = 0.01), - the relative clearance was significantly slower and the hepatic CYPs concentration lower than in non-diabetic controls (p < 0.01) | Wadhwaan et al. (2003), Case-control study |
| Diabetes patients with normal liver vs. healthy subjects | antipyrine (CYP1A2), 2B6, 2C8, 2C9, 2C18 and 3A4 | 4 = diabetes, 13 = controls | - half-life was reduced by 44% compared to the controls (p = 0.002), whereas the resulting plasma clearance did not differ between diabetes patients with normal liver compared to controls | Taussig et al. (1984), Case-control study |
| Type I and type II diabetes vs. controls | antipyrine (CYP1A2), 2B6, 2C8, 2C9, 2C18 and 3A4 | 30 = diabetes (15 T1D and 15 T2D), 21 = controls (12 for T1D and 9 for T2D) | - half-life in reduced by 44% compared to the controls (p = 0.002), whereas the resulting plasma clearance did not differ between controls and type I diabetes (T1D), - Type II diabetes (T2D) showed a 31% increase in plasma half-life (p = 0.03) and they had a significant decrease in corresponding clearance (p = 0.02) | Danalik et al. (2001), Case-control study |
| Type I and type II diabetes vs. controls | antipyrine (CYP1A2), 2B6, 2C8, 2C9, 2C18 and 3A4, caffeine (CYP1A2) and dextromethorphan (CYP2D6) | 15 = T1D, 16 = T2D, 16 = controls | - metabolism was significantly higher in T1D patients than in the patients with T2D and in healthy volunteers, - no change in metabolism between T2D and controls, - CYP1A2 activity was 34 and 42% higher in patients with T1D compared with controls and patients with T2D respectively but those changes did not reach the statistical significance (p = 0.11), - no change between groups concerning the CYP2D6 phenotype distribution | Matzke et al. (2004), Case-control study |
| Type II diabetes vs control | caffeine (CYP1A2) supramax (CYP2B6), tobutamide (CYP2D6), omeprazole (CYP2C19), dextromethorphan (CYP2D6), chlorzoxazone (CYP2E1) and CYP3A (midazolam) | 38 = T2D, 35 = control | - metabolic activity of CYP1A2 was significantly increased in T2D patients compared to control (p = 0.01), - but when the 19 diabetic patients who are under insulin injection were removed, the difference was no longer significant (p = 0.12) | Lucía et al. (1998), Case-control study |
| Insulin dependent (ID) diabetes patients vs. control T1D and T2D vs. control | caffeine (CYP1A2) and dabirisoquin (CYP2D6) | 28 = ID diabetes patients, 22 = healthy volunteers | - no significant differences for CYP2D6 activity and a significant increase in CYP1A2 activity in diabetes patients (p = 0.0001) | Wang et al. (2003), Case-control study |
| Diabetic vs. controls | tobutamide (CYP2D6) | 10 = diabetic patients, 7 = control | - the apparent volume of distribution, apparent clearances, half-life, and peak concentrations of caffeine did not differ between both type of diabetes and controls | Motassai et al. (2018), Case-control study |
| Diabetes mellitus vs. controls | paracetamol (CYP2E1) | 19 = diabetes mellitus, 10 = healthy volunteers | - half-life was significantly increased (p < 0.001) with a corresponding decrease in clearance (p < 0.001) when compared with healthy volunteers, - clearance in patients with T2D were decreased compared to T1D patients (p = 0.001) but it was not the case for its half-life, - the distribution volume was increased in patients with T1D compared to patients with T2D (p = 0.09) | Kompani et al. (1995), Case-control study |
| Type II diabetes vs control | antidiapine (CYP3A) | 15 = T2D, 20 = control | - no significant difference in AUC in hypertensive patients with and without T2D | Schot et al. (1988), Case-control study |
| Type II diabetes vs control | nisoldipine (CYP3A) and lidocaine (CYP3A) | 17 = T2D, 10 = control | - the apparent clearances of both nisoldipine enantiomers in the hypertensive patients with T2D are significantly lower than in hypertensive control patients (p = 0.05), - higher ratio of plasma lidocaine/MEX concentration for diabetic group than in control group (p < 0.05), - means that CYP3A4 activities were decreased in the diabetic groups, - significant correlations were found (p = 0.05) between the MR of lidocaine and the apparent clearance of nisoldipine enantiomers obtained for both groups | Um Y et al. (2016), Case-control study |
| Diabetes vs. control | CyA (CYP3A) | 7 = diabetes, 10 = control | - No difference was found in daily dose needed between both groups (p = 0.55) but metabolite-parent concentration ratios for all metabolites except one (AM4N, p = 0.90) were significantly lower in diabetic patients (0.0001 < p < 0.04) (Continued on following page) | Iida et al. (1977), Case-control study |
In Lenoir et al. (2021), downregulation is proportional to disease severity and that inflammation characterized by CYP substrates, explained totally or partially by modulation of CYP activity. Furthermore, there were no difference between healthy controls and Crohn’s disease patients in remission, implying that CYP downregulation is proportional to disease severity and that recovery resulted in a return to baseline metabolic activity (Sanee et al., 2011). Norverapamil goes through the same process and it is expected that the enantiomers ratio of norverapamil to verapamil remains unchanged (Sanee et al., 2011).

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|--------------------------------|--------------------|---------------------------------|-----------------------|
| Diabetes vs. control          | CyA (CYP3A)                    | 8                  | AUC adjusted with dosage was significantly lower in diabetic group (p = 0.03) | Baer et al. (1986), Case-control study |
| Type I and II diabetes vs control | chloroquine (CYP2E1)            | 7                  | no difference was found concerning dose and through levels | Smolen et al. (2016), Case-control study |
| Type I diabetes vs. control   | quinidine (CYP3A)              | 12                 | PK parameters were comparable in the two groups (p = 0.02) | Mayo et al. (2003), Case-control study |
| Type I and II diabetes vs control | chloroquine (CYP2E1)            | 14                 | 2-fold increase in the oral clearance (p < 0.05) in T2D patients compared with T1D and controls |Daneshzadeh et al. (2006), Case control study |
| Type 1 and type II diabetes   | antipyrene (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A4) | 130 = T1D (120 = controls), 99 = T2D (80 = controls) | clearance decreased in T2D patients as compared to controls, - metabolism is rapid in T1D patients |Goklay et al. (2015), Case-control study |
| Type 1 diabetes vs controls   | theophylline (CYP1A2)           | 8                  | mean plasma clearance and elimination half-life did not differ significantly between the 2 groups |Sanee et al. (2011), Case-control study |
| Gestational diabetes vs. pregnant women | metoprolol (CYP2D6)           | 10                  | PK of the metoprolol isomers in the pregnant women and in gestational diabetes groups did not differ significantly, except for the R-metoprolol half-life (p < 0.05) | Schneider et al. (1976), Case-control study |
| Gestational diabetes vs. pregnant women | lidocaine (CYP3A)             | 6                  | the ratios of lidocaine and its metabolite MEGX concentrations (lidocaine/MEGX ratio) at 15 and 30 min were significantly higher in the pregnant women with gestational diabetes mellitus compared to the normal pregnant women (58.34 vs. 23.21 at 15 min and 37.52 vs. 15.80 at 30 in, p < 0.05) |Labwoh et al. (2016), Case-control study |
TABLE 10 | Impact of autoimmune diseases on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|--------------------|--------------------------------|-----------------------|
| Psoriasis vs healthy volunteers | venlafaxine (CYP2D6)           | 13 = psoriasis, 11 = control | - PK of the enantiomers and of its metabolites were not altered as compared to control | Lang et al. (1996) Case-control study |
| Systemic lupus erythematosus (SLE) vs. healthy controls | debrisoquin (CYP2D6) | 42 = SLE, 147 = control | - In patients with SLE, there is an inhibition in the metabolism of debrisoquin compared to controls because there is significantly more PM patients in patients group (p < 0.04) | Tidball (2005), Case-control study |
| Proctitis vs healthy volunteers | /                             | 11                 | - patients who suffered from proctitis showed a lower CYP2E1 and 3A4 gene expression in rectal mucosa with severe inflammation compared to normal mucosa (p < 0.05), - no significant difference for CYP3A4 (p = 0.08) | Baigrie et al. (1992), Cohort study |
| Behçet’s disease vs. healthy subjects | losartan (CYP2C9) | 52 = Behçet’s disease, 73 = control | - the MR (losartan/E-3174) significantly increase (p = 0.0032) compared to controls already included who genetic variants and losartan oxidation were already known, - in patients with the wild type CYP2C9 genotype (1A1/1), the MR significantly increased in patients with Behçet’s disease compared to controls (p = 0.006) but there is no significant differences found for other CYP2C9 genotype | Bergin et al. (2011), Case-control study |
| Rheumatoid arthritis (RA) vs. healthy volunteers | verapamil (CYP3A4, 1A2, 2C8, 2C9 and 2C19) | 8 = RA, 8 = controls | - less metabolized and bound to protein in patients with RA compared to controls, - AUC of verapamil and norverapamil were significantly higher in patients with RA as compared to controls thus, there is no changes in metabolite to parent drug ratio | Haas et al. (2003), Case-control study |
| Active and controlled rheumatoid arthritis vs healthy subjects | losartan (CYP2C9) | 14 = active RA, 12 = controlled RA, 12 = controls | - PK not significantly altered but AUC of its pharmacologically active metabolite was significantly decreased, - MR exhibited a significant correlation with disease severity (r = −0.35, p < 0.006) | Lenoir et al. (2020), Case-control study |
| Rheumatoid arthritis | /                             | 49 = RA             | - cytokines such as TNF-α, IL-1β and IL-17 increase the CYP7B activity in synovial tissue, - TGF-β down-regulate the CYP7B activity and it results in enhanced formation of 7α-OH-DHEA in the arthritic joint, which may contribute to the maintenance of the inflammation and, thus, the chronicity of the inflammation response | Mostowik et al. (2015), Cohort study |
| active Crohn’s disease (CD), Crohn’s disease in remission and healthy subjects | verapamil (CYP3A4, 1A2, 2C8, 2C9 and 2C19) | 22 = CD remission, 14 = CD active, 9 = controls | - plasma S-verapamil concentration in patients with active CD was significantly higher than in both healthy controls and patients in CD remission (p < 0.001) but not between healthy controls and Crohn’s disease remission, - same tendency was seen for R-verapamil but there is no statistical significance, - as in RA patients, the ratio AUC of both S and R norverapamil over their corresponding verapamil enantiomers were not significantly different among the 3 groups of subjects, - there was no higher PD response in patients due to higher verapamil level | Bernlochner et al. (2010), Case-control study |
| Crohn’s disease vs. control | propranolol (CYP2D6)          | 10 = Crohn’s disease, 12 = Crohn’s disease than those of the controls (p < 0.05) | - levels were significantly higher in the 10 patients with Crohn’s disease than those of the controls (p < 0.05) | Harvey and Morgan (2014), Case-control study |
| Celiac disease | /                             | 9                  | - reduction in the intestinal content of CYP3A in patients with celiac disease before treatment patients with a gluten-free diet and increase in intestinal CYP3A protein after the diet | Kacevska et al. (2008), Cohort study |

Celiac disease is an autoimmune disease that is triggered by an immune response to gluten and may result in increased morbidity or mortality (Lebwohl et al., 2018). The reduction in intestinal CYP3A content during celiac disease and its increase after a gluten-free diet indicate that local inflammation reduced CYP3A activity but that it returns to baseline with disease improvement (Lang et al., 1996).
TABLE 11 | Impact of surgery on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|--------------------|--------------------------------|-----------------------|
| Surgery                       | clozapine (CYP1A2)           | 49-year-old man    | - clozapine and norclozapine levels were reduced due to persistent sedation | Luong et al. (2016), Case reports |
| (a) Surgery                   | /                             | 16 (5 a, 6 b and 5 c) | - ERMBT results significantly declined in all groups compared with before surgery | Chen et al. (1994) |
| abdominal aortic bypass graft | carbon-14 [14C] ERMBT (CYP3A) |                    | - a trend toward difference in ERMBT results between surgery but didn’t reach statistical significance (p = 0.06) | Cohort study |
| colon resection               |                                |                    | - the nadir ERMBT result was significantly and negatively correlated (r = -0.541, p = 0.03) with peak IL-6 concentration | |}
| peripheral vascular bypass graft | caffeine (CYP1A2), bupropion (CYP2B6), flurbiprofen (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6) and midazolam (CYP3A) | 30 | - test results were significantly different if patients IL-6 peak concentration was IL-6 > 100 pg/ml or <100 pg/ml (35.6 vs. 74.7%, p < 0.001) | Rivory et al. (2002), Cohort study |
| Hip surgery                   | clopidogrel (bioactivated by CYP2C19) | 50 | - CYP2C19 and 3A MR decreased by 57% (p = 0.0002) and 61% (p ≤ 0.0001) respectively with the nadir at D3, - CYP1A2 MR decreased by 53% (p ≤ 0.0001) with the nadir at D1, - CYP2B6 and 2C9 MR increased by 120% (p < 0.0001) and 79% (p = 0.0018), respectively and peaked at d1, - No change in CYP2D6 MR | Alexandre et al. (2007), Cohort study |
| percutaneous coronary intervention | clopidogrel (bioactivated by CYP2C19) | 1′223 | - prolonged post-angioplasty increase is associated with lower platelets’ response to clopidogrel | Charles et al. (2006), Cohort study |

Surgery

The impact of surgery on concomitant treatment and analgesia management has been assessed in several studies (Table 11). Surgery is associated with an inflammatory response due to muscle or tissue injury to induce repair, regeneration and growth and so inflammatory markers increase after surgery, but not equally (Tidball, Stavropoulou et al., 2018). IL-1β was only detected during the early perioperative period and for a very short time (Baigrie et al., 1992). IL-6 plasma level peaked 4-48 h after surgery and declined drastically by 48-72 h in all patients without any postoperative complication (Baigrie et al., 1992). CRP level rose more slowly postoperatively compared with the cytokine levels (IL-6, TNF-α and IL-1β) (Bergin et al., 2011). Acute inflammation after elective surgery was associated with a significant decrease in CYP3A metabolic activity (Haas et al., 2003). A recent study with a cocktail approach has concluded that there is an isoform specific impact of inflammation on CYP activities (Lenoir et al., 2020). Indeed, this study showed that CYP1A2, CYP2C19 and CYP3A activities decreased significantly by 53, 57 and 61%, whereas CYP2B6 and CYP2C9 activities increased significantly by 120 and 79% (Lenoir et al., 2020). However, surgery did not significantly impact CYP2D6 activity (Lenoir et al., 2020). These findings were confirmed by a case report that showed a toxic increase in clozapine levels 4 days after surgery and by authors who further showed that clopidogrel efficacy was reduced in patients undergoing percutaneous coronary intervention, because clopidogrel must be bioactivated by CYP2C19 to be effective (Bernlochner et al., 2010; Leung et al., 2014; Mostowik et al., 2015).

Cancer

Inflammation is linked to all stages of cancer (risk of development, initiation, invasion, metastasis and mortality) as highlighted in Table 12 (Harvey and Morgan, 2014). Certain immune-mediated diseases have been associated with cancer such as inflammatory bowel disease (IBD), chronic infection by Helicobacter pylori and chronic psoriasis associated with an increased risk of colorectal, gastric and skin cancer, respectively (Harvey and Morgan, 2014). The first pro-cancer immune signals are via tumor cells that successively produce cytokines and act to increase transcription factors, induce epigenetic changes and initiate angiogenesis (Harvey and Morgan, 2014). Cytokines are involved from neoplastic transformation of cells to tumor progression and metastasis, and are thus involved in several cellular events leading to cancer (Kacvská et al., 2008). These signals and others induced to respond to cancer are opposed by antigen-presenting cell-mediated anticancer immune responses (Harvey and Morgan, 2014). Moreover, the greater the antitumoral response is, the more the cancer outcome is improved whereas some T-cells subsets are associated with tumor promotion (Harvey and Morgan, 2014). Some cytokines have tumor-promoting, antitumor effects or both (Kacvská et al., 2008). Some cytokines could be produced by the tumor itself.
TABLE 12 | Impact of cancer on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by                                           | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction                                                                 | References and design |
|-------------------------------------------------------------------------|-------------------------------|--------------------|------------------------------------------------------------------------------------------------|-----------------------|
| Liver metastasis before cytostatic treatment vs. healthy controls       | antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4) | 12 = liver metastasis, 12 = controls | - no significant difference between patients with liver metastases before cytostatic treatment and controls | Williams et al. (2000), Case-control study |
| Bone marrow transplantation for haematological malignancies (radiation and chemotherapy) | CyA (CYP3A)                  | 6                  | - concentration peak value occurred 15.8 days after bone marrow transplantation and it’s corresponded to a 3- or 4-fold increase relative to the steady state day (p > 0.015). - CyA concentration peak and IL-6 peak levels are interdependent because there was a correlation between these two parameters (r = 0.794, p = 0.03) | Burns et al. (2014), Cohort study |
| Cancer                                                                  | ERMBT (CYP3A)                 | 40                 | - patients with CRP >10 mg/L had an average 30% reduction in CYP3A4 metabolic activity (p = 0.0002), - 1/Tmax values were negatively correlated with both CRP (r = −0.64, p < 0.000001) and α-glycoprotein (r = −0.45, p < 0.005), - 3 patients were treated by a CYP3A4 inhibitor while 4 patients were on long-term treatment with dexamethasone (inducer) but correlation with CRP remained significant (r = −0.55, p = 0.002) after removal of these patients | Helsby et al. (2008), Cohort study |
| Advanced cancer patients with normal liver function                     | midazolam and docetaxel (CYP3A) | 56                 | - high midazolam concentration and free docetaxel AUC were associated with sever neutropenia (and conversion to febrile neutropenia), - high midazolam concentration was correlated with elevated ferritin level (r = 0.32, p = 0.02) (indicator of an inflammatory state), - according to authors, inflammation favors a reduction in CYP3A activity and thus, could lead to an overexposure to its substrates | Yasu et al. (2017), Cohort study |
| Advanced cancer patients who were suitable for palliative chemotherapy   | docetaxel (CYP3A)             | 68                 | - occurrence of grade 3/4 non-haematological toxicities were not associated with high docetaxel exposure but with baseline concentrations of AAGP (p = 0.03) and CRP (p = 0.05), - results from correlation analysis between inflammation markers and docetaxel clearance were not given, as the results from EBT CYP2C19 activity differed significantly (p < 0.0001) in the EM cancer patients compared of the References population with EM genotype | Mafuru et al. (2019), Non-randomized clinical trial |
| Cancer patients vs healthy subjects                                     | omeprazole (CYP2C19)          | 16 = cancer, 77 = controls | - significant discordance between the CYP2C19 activity predicted by genotype and the measured phenotype (p < 0.0001), - no significant difference in CRP and IL-6 concentrations between discordant and concordant subjects (p = 0.072 and p = 0.694, respectively) | Picotti et al. (1998), Case-control study |
| Multiple myeloma                                                        | proguanil (CYP2C19)           | 25                 | - comparison of the predicted phenotype from genotype and the measured MR of CYP2C19 found a statistically discordance (p < 0.0005), - of the 30 cancer patients with genotypic EM status, 11 were CYP2C19 PM, - no significant correlation between the levels of any individual cytokine (CRP, IL-1β, IL-6, TNF-α, TGF-β3 and CRP) and CYP2C19 metabolic activity | Eikahwaj et al. (1999), Cohort study |
| Advanced cancer                                                         | omeprazole (CYP2C19)          | 31                 | - CRP levels were significantly correlated (r = 0.22, p < 0.001), - higher voriconazole trough concentration >1.0 ug/ml was observed in higher CRP level >4 mg/dL | Israel et al. (1993), Cohort study |
| Hematopoietic cell transplantation                                       | voriconazole (CYP3A4 and CYP2C19) | 67                 | - no signification difference between patients with liver metastases before cytostatic treatment and controls | Jonkman et al. (1989), Cohort study |

(Continued on following page)
TABLE 12 | (Continued) Impact of cancer on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|------------------------------|--------------------------------|--------------------|-------------------------------|-----------------------|
| Hematologic patients         | voriconazole (CYP3A4 and CYP2C19) | 113                | - concentration was significantly correlated with IL-1β in acute myeloid (r = 0.456, p < 0.0001), acute lymphoblastic (r = 0.317, p = 0.019), and chronic myeloid leukemia (r = 0.737, p = 0.04), - concentration and TGF-β1 were correlated (r = 0.436, p < 0.001) in acute myeloid leukemia patients only, - according to authors, IL-6 level could partially predict the voriconazole trough concentration because these two factors were weakly inversely correlated in hematologic patients regardless of underlying disease | Williams et al. (1987), Cohort study |
| Hepatocellular carcinoma     | phenacetin (CYP1A2)             | 148 = carcinoma, 82 = controls | - clearance did not significantly differ between the healthy participants and patients with hepatocellular carcinoma | Schoergenhofer et al. (2018), Case-control study |

(Kacevska et al., 2008). Inflammation has therefore a pivotal role in cancer and the proliferation of malignant cells by a dynamic equilibrium in the tumor environment (Harvey and Morgan, 2014). Cytokines present in the tumor environment are also launched in the systemic circulation and have general effects on the function of distant organs such as the liver (Kacevska et al., 2008). Inflammatory markers levels are dependent on tumor types, but high level of CRP, IL-6, IL-1β have been associated with poor prognosis (Kacevska et al., 2008). Some results suggest that high IL-6 is associated with decreased CYP3A metabolic activity but can also nonspecifically downregulate CYP-dependent drug metabolism (Chen et al., 1994). CRP and α-glycoprotein were also negatively correlated with CYP3A activity and cancer patients with significant acute-phase response may have reduced CYP3A drug metabolism, which may have implications for the safety and efficacy of chemotherapy (Rivory et al., 2002; Charles et al., 2006; Alexandre et al., 2007). Inflammatory status and lymphocyte count should thus be included in the evaluation of the benefit/risk ratio before the initiation of a cytotoxic chemotherapy (Alexandre et al., 2007). Concerning CYP2C19, studies showed that CYP2C19 activity was not solely predicted by the genotype in cancer patients (Williams et al., 2000; Helsby et al., 2008; Burns et al., 2014). Indeed, CYP2C19 activity was reduced in cancer patients, with a discordance between the measured phenotype and the predicted phenotype from the genotype. However, no significant correlation was found between CYP2C19 activity and the levels of cytokine, whereas this was the case for voriconazole through concentration (Helsby et al., 2008; Burns et al., 2014; Yasu et al., 2017; Mafuru et al., 2019). The mechanism behind the decrease of CYP2C19 activity observed in cancer patients may be related to the inflammatory response even though it remains debated (Helsby et al., 2008; Burns et al., 2014; Yasu et al., 2017; Mafuru et al., 2019). Other authors showed that cancer has no impact on CYP1A2 metabolic activity as compared to liver disease or infection (Wang et al., 2010).

Therapies With Immunomodulator, anti-TNF-α and -Mabs

As biological therapies aim to decrease the underlying inflammation of the disease, interleukins (IL) injections are expected to have an impact on CYP activity, as underlined in Table 13. As an example, IL-2 doses of 9–12 × 10⁶ units daily may downregulate CYP activities in patients with HIV infection and cancer in whom this treatment is administered to boost the immune system (Piscitelli et al., 1998; Elkahwaji et al., 1999). Conflicting results exist regarding IFN administration, with a discrepancy between acute and chronic treatment (Williams and Farrell, 1986; Williams et al., 1987; Jonkman et al., 1989; Israel et al., 1993; Hellman et al., 2003; Sulkowski et al., 2005; Gupta et al., 2007; Furlanet et al., 2010; Brennan et al., 2013). However, case reports and more specific studies assessing CYP metabolic activity lean toward CYP downregulation and care must be taken to avoid interactions and ADRs (Craig et al., 1993; Adachi et al., 1995; Serratrice et al., 1998; Hassan et al., 1999; Becquemont et al., 2002). The level of anticoagulation should be closely monitored when interferon is given together with warfarin, as it appears that CYP are downregulated (Adachi et al., 1995; Serratrice et al., 1998). Additionally, the timing of IFN-α administration relative to concomitant chemotherapy should be considered to avoid a decrease in CYP3A4 and 2B6 activity and thus to achieve better efficacy (Hassan et al., 1999). For example, interferon-α-2b inhibits CYP1A2, 2D6 and 2C19 and these findings pose new challenges for patients on these therapies with respect to PK interaction with concomitant drugs commonly used (Islam et al., 2002). Further studies are needed to measure the impact of IFN and new cytokine therapies coming on the market on CYP activities. Cytokines act on CYP in an isofrom-specific manner, and it is likely that IFN or IL modulate different CYP while they have no impact on others. Moreover, it is crucial to understand whether the modulation of CYP activity is due to this kind of therapy, to the underlying disease which may be inflammatory,
TABLE 13 | Impact of therapies with immunomodulator on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|--------------------------------|---------------------|-------------------------------|-----------------------|
| Treatment with IL-2           | indinavir (CYP3A)              | 8 = HIV seropositive patients (observational), 9 = HIV seropositive patients (prospective) | - in the HIV seropositive-patients, the mean concentration of indinavir was significantly increased on day 5 of IL-2 therapy, - in the nine HIV seropositive-patients, the mean indinavir AUC increased significantly by 88% between day 1 and day 5 of IL-2, - mean IL-6 concentrations during IL-2 therapy increased between day1 and day5 from 4- to 86-fold, - study combines observations made in one observational and one prospective (as part of a phase II trial) studies | Williams and Farrell (1986), Cohort study and non-randomized |
| Treatment with IL-2           | /                              | 5 = 3 or 6x10⁶/m² units of IL-2, 6 = 9 or 12x10⁶/m² units of IL-2, 7 = 0 units of IL-2; Patients with cancer | - in non-tumorous liver fragment removed with the tumor in each patients, authors observed that CYPs proteins (CYP1A2, 2C, 2E1 and 3A), monoxygenase activities of methoxyresorufin and erythromycin and total CYPs were significantly decreased only in the group of patients treated with highest doses of IL-2, compared to control | Furlanut et al. (2010), Randomized clinical trial |
| Treatment with IFN-α          | theophylline (CYP1A2), antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A), hexobarbitone (CYP2C19) | 7 | - no significant difference in TNF-α, IL-1β, IL-6 and CRP activities after both acute (initiation) and chronic (2 weeks) IFN-α injections compared to baseline, except for TFN-α activity that significantly decreased after chronic therapy, - significant effects of acute IFN-α administration on the oral clearance of the three probe drugs were not detected, - chronic exposure to IFN-α was associated with a significant lowering clearance (33% compared with baseline, p < 0.05) but no significant correlations were observed between the changes in theophylline clearance and changes in serum cytokines or acute phase proteins, - chronic IFN-α therapy decreased antipyrine oral clearances by 20% but this did not reach statistical significance and it appeared to have no effect on the metabolism of racemic hexobarbitone - after IFN-α treatment in healthy volunteers, there were significant 10–15% increases (p < 0.05) in the terminal elimination half-life and AUC of aminophylline administered intravenously, - the total clearance showed a comparable decrease (p < 0.05) | Sulkowski et al. (2005), Cohort study |
| Treatment with IFN-α          | aminophylline (CYP1A2)         | 12 = healthy volunteers | - significant difference in TNF-α, IL-1β, IL-6 and CRP activities after both acute (initiation) and chronic (2 weeks) IFN-α injections compared to baseline, except for TFN-α activity that significantly decreased after chronic therapy, - significant effects of acute IFN-α administration on the oral clearance of the three probe drugs were not detected, - chronic exposure to IFN-α was associated with a significant lowering clearance (33% compared with baseline, p < 0.05) but no significant correlations were observed between the changes in theophylline clearance and changes in serum cytokines or acute phase proteins, - chronic IFN-α therapy decreased antipyrine oral clearances by 20% but this did not reach statistical significance and it appeared to have no effect on the metabolism of racemic hexobarbitone - after IFN-α treatment in healthy volunteers, there were significant 10–15% increases (p < 0.05) in the terminal elimination half-life and AUC of aminophylline administered intravenously, - the total clearance showed a comparable decrease (p < 0.05) | Gupta et al. (2007), Non-randomized |

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TABLE 13 | (Continued) Impact of therapies with immunomodulator on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|--------------------|--------------------------------|-----------------------|
| Treatment with IFN            | theophylline (CYP1A2)         | 5 = hepatitis B, 4 = healthy subjects | - a reduction of theophylline elimination was observed in 8 subjects (remaining subject was a healthy control) and was ranged from 33 to 81%, compared to initial theophylline clearance study, - no impact of the hepatitis on these results because there was no clinical or biochemical change in the liver disease, - a second theophylline clearance study was done 4 weeks after the interferon’s injection and it was back to initial value | Hellman et al. (2003), Non-randomized |
| Treatment with IFN-α          | antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18 and 3A) | 5 = hepatitis B, 4 = healthy subjects | - recombinant leukocyte α-interferon reduced the antipyrine clearance by 16% (p < 0.01) and the half-life increased but this was not significant | Brennan et al. (2013), Non-randomized |
| Treatment with IFN-α          | warfarin (CYP2C9)             | 52 year-old-woman | - her prothrombin time increased to 16.7–20.4 s with a rise in serum warfarin concentration from <0.8 μg/ml to 5.2 μg/ml 10 days after the onset of IFN-α therapy, - dose was reduced and both anticoagulation and serum warfarin concentration had returned to nearly baseline values | Adachi et al. (1995), Case report |
| Treatment with IFN-α-2b        | acenocoumarol (CYP2C9)        | 46-year-old-woman | - at the beginning of the treatment, anticoagulant effect of acenocoumarol increased (thrombotest decreased from 30–35–19%), - when IFN-α-2b dosage decreased because of infection remission, anticoagulant effect decreased (thrombotest increased from 25–40–69%), - it led to the adaptation of the dosage of acenocoumarol to be on thrombotest range, - anticoagulation level decreased from 1 day after injection to 2 or 3 days later | Serratrice et al. (1998), Case report |
| Treatment with IFN-α-2b        | ERMBT (CYP3A)                 | 6 = chronic hepatitis C, 4 = healthy controls | - ERMBT before and 20–26 h after IFN-α-2b injection, - IFN-α-2b induced a small significant decrease in ERMBT (p < 0.05), - at baseline CYP3A4 activity was lower in patients with hepatitis C but the effect of IFN appeared to be not different | Craig et al. (1993), Non-randomized |
| Treatment with IFN-α          | cyclophosphamide (CP) (CYP2B6 active metabolite and CYP2C9, 2C19 and 3A substrate) | 10                          | - administration of IFN-α before CP caused a 63% decrease in its clearance (p = 0.004) compared to an administration of IFN-α 24 h after CP, - there is a 45% decrease in exposure of CP active metabolite’s (4-OHCP) when IFN-α was administered before CP, expressed as AUC (p = 0.002), compared with that observed when IFN-α was administered 24 h after CP, - this resulting in a greater decrease in leukocyte count (45%, p = 0.02) when IFN-α was given after CP in the 10 patients with multiple myeloma | Hassan et al. (1999), RCT |

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**TABLE 13 (Continued) Impact of therapies with immunomodulator on CYP substrates, explained totally or partially by modulation of CYP activity.**

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|-------------------|-------------------------------|-----------------------|
| Treatment with IFN-α-ribavirin | dextromethorphan (CYP3A4 and CYP2D6), by measuring different metabolite) and caffeine (CYP1A2) | 14 | - mean CYP3A4 activity increased from 0.18 ± 0.06 in patient with HCV before beginning of IFN-α-ribavirin treatment to 0.48 ± 0.33 1 month after but this did not reach statistical significance (p = 0.19) - a similar evolution of CYP2D6 activity could be observed during the first month of treatment (148 ± 0139 to 421 ± B41, p = 0.08), - CYP1A2 activity did not changed, going from 0.39 ± 0.11 before treatment to 0.32 ± 0.13 after 1 month, - pretreatment CYP3A4 and CYP2D6 activities of the 14 studied patients were significantly lower than those observed in 35 healthy volunteers (p = 0.0006 and p = 0.0008 respectively), - after 1 month of antiviral treatment, CYP3A4 and 2D6 did not differ significantly from those in healthy volunteers, probably because of the recovery of HCV patients | Becquemont et al. (2002), Non-randomized |
| Treatment with IFN-α-2b | caffeine (CYP1A2), mefenoxymetin (CYP2C19), debrisoquin (CYP2D6), chloroxazone (CYP2E1) and dapsone (CYP2C8 and CYP2C9) | 17 = patients with high-risk resected melanoma | - IFN-α-2b inhibits immediately the activity of CYP1A2 (p = 0.001) and 2D6 (p < 0.001) in patients with high-risk resected melanoma, - inhibition of CYP2C19 was detected for the first time at day 28 (p < 0.001) after the initiation of high-dose IFNα-2b treatment (20 MU/m2/day i.v for 5 days/weeks during 4 weeks and 10 U/m2/day s.c for 3 days/week x 48 weeks), - no significant inhibition was seen for CYP2E1 | Islam et al. (2002), Cohort study |
| Treatment with peginterferon-α-2b | dextromethorphan (CYP2D6) and, fluoxetine (CYP2D6 active metabolite) | 20 | - MR before and after initiation of peginterferon-α-2b and ribavirin therapy go from 0.10 ± 0.40 to 0.04 ± 0.09 and that’s mean that metabolite production of dextromethorphan increased after hepatitis C, but it is not significant (p = 0.087), - mean serum concentrations of fluoxetine and its metabolite (norfluoxetine) at baseline and 2 months later during combined antiviral treatment didn’t change significantly, - only the half-life of fluoxetine showed a significant reduction during combined antiviral therapy (p = 0.014) | National Center for Biotechnology Information (2012), Cohort study |
| Treatment with peginterferon-α-2a | methadone (CYP3A, 2C8 and 2D6) | 24 with hepatitis C | - treatment did not alter the pharmacokinetic of methadone in patients, - increase exposure of total methadone by 10–15% was not statistically significant | Wu and Fleming (2011), Non-randomized |
| Treatment with peginterferon-α-2b | methadone (CYP3A, 2C8 and 2D6) | 20 with hepatitis C | - a barely significant increase in total methadone exposure of 15–16% was observed after 4 weekly injection of peginterferon-α-2b - this increase was not clinically significant because there were no symptoms of methadone overdose | Ling et al. (2009), Non-randomized |

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TABLE 13 | (Continued) Impact of therapies with immunomodulator on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|---------------------|---------------------------------|------------------------|
| Treatment with peginterferon-α-2a | theophylline (CYP1A2), tolbutamide (CYP2C9), mephenyton (CYP2C19), debrisoquin (CYP2D6) and dapsone (CYP3A) | 14 | - theophylline AUC increased significantly but C/F difference was not significant, - no effect on the PK of any other probe drug (S)/(R) mephenyton ratio (p = 0.5) and debrisoquin MR (p = 0.4) were not statistically significant different before and during regular INF-β treatment | Schmitt et al. (2011), Cohort study |
| Treatment with INF-β | mephenyton (CYP2C9 and 2C19 and induces 2C9, 2C19 and 3 A) and debrisoquin (CYP2D6) | 10 with multiple sclerosis in the first stage | | Zhuang et al. (2015), Non-randomized |

or to its resolution by these same therapies (reduction of inflammation caused by the disease).

The impact of mabs therapies are summarized in Table 14. Monoclonal antibodies have a high degree of specificity against an antigen or an epitope (National Center for Biotechnology Information, 2012). In 2018, more than sixty therapeutic monoclonal antibodies were approved and used in the United States for their action against specific immune cells such as lymphocytes and cytokines or against specific enzymes, cell surface transporters or signaling molecules (National Center for Biotechnology Information, 2012). Consequently, a number of studies have examined the impact of monoclonal antibodies on CYP metabolic activity, assuming that these drugs, by reducing inflammation, return CYP metabolic activity to baseline (Ling et al., 2009; Schmitt et al., 2011; Wu and Fleming, 2011; Zhuang et al., 2015; Tran et al., 2016; Lee et al., 2017; Wen et al., 2020) (Table 14).

A return to baseline level after treatment of inflammation was not always observed (Wollmann et al., 2017; Davis et al., 2018). A lag was observed in some cases, such as basiliximab coadministration, which increased tacrolimus through concentration on day 3 but decreased on day 30 (Sifontis et al., 2002). Moreover, OKT3 (also known as muromonab, a CD3 receptor antibody) treatment transiently increased CyA through concentration, and authors suggested that OKT3 inhibits CYP3A4 metabolic activity by inducing transient cytokine release (Vasquez and Pollak, 1997). No changes were observed in drugs PK parameters before and after monoclonal antibodies administration, possibly because CYP metabolic activity was similar in psoriasis disease and in healthy volunteers (Bruin et al., 2019; Khatri et al., 2019). However, these therapies are used for a variety of diseases, with different levels of proinflammatory markers. In addition, a recently published study assessed the impact of clazakizumab, an anti-IL-6 antibody, in kidney transplant recipients with antibody-mediated rejection (ABMR) on CYP3A and CYP2C19 activity by pantoprazole and on tacrolimus and CyA concentrations (Mühlbacher et al., 2021). In contrast to earlier observations, prolonged blockade of IL-6 did not enhance CYP metabolism (Mühlbacher et al., 2021). This could be because the included patients did not have systemic inflammation before initiation of clazakizumab, with IL-6 and CRP levels in the normal range (Mühlbacher et al., 2021). Thus, clazakizumab did not increase CYP metabolism because the included patients had unaltered CYP expression, as ABMR may be different from other disease states, such as infection or autoimmune disease, where systemic inflammation is present (Mühlbacher et al., 2021).

**DISCUSSION AND PERSPECTIVES**

Our systematic review identified 218 publications that evaluated the impact of inflammation on CYP activities which we divided into 17 sources of inflammation. Indeed, current literature suggests that cytokine signalling pathways differ according to the trigger of inflammation, leading to heterogeneous effects on CYP activity, with different magnitude, potency and time-course (de Jong et al., 2020; Stanke-Labesque et al., 2020). This analysis allowed us to identify areas where the literature is abundant, such as infections like pulmonary infection, hepatitis or HIV and for some therapeutic agents like immunosuppressants or clozapine, and others where further research is needed, such as for autoimmune diseases, and other specific diseases such as diabetes or the anti-inflammation treatments.

Our analysis also identified that studies should be more specifically conducted to assess whether resolution of inflammatory episodes allows a return to baseline of CYP activities. Indeed, inflammatory diseases are chronic, but with a possibility of remission, and acute inflammatory events can punctuate life (infection, surgery, cancer...). A better understanding of the mechanisms of modulation and return to the initial state would make it possible to anticipate changes in the PK of concomitant treatments at different phases of the disease or of the patient’s life. This could be done through the impact of anti-inflammatory treatments as well as monoclonal antibody therapies. These therapies are relatively new and much remains to be discovered, but they are highly targeted, and the impact of these different molecules could be isoform specific.

Our literature review highlighted the different effect of inflammation according to the CYP considered. Several studies have investigated the impact of infection on drugs of the nervous systems, mainly CYP2D6 substrates without always showing a significant impact. It now appears that CYP2D6 activity is not modulated by inflammation and this is confirmed in chronic hepatitis C patients where downregulation is linked to the presence of liver kidney microsomal type 1 (LKM-1) antibodies (Girardin et al., 2012). LKM-1 antibodies are often produced during chronic HCV infection and appear to be...
| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|-------------------------------|--------------------|--------------------------------|-----------------------|
| Basiliximab                   | tacrolimus (CYP3A)            | 12 = treatment, 8 = control | - 63% increased tacrolimus trough concentration in basiliximab group at day 3 vs controls ($p<0.05$). - tacrolimus through concentration decreased in basiliximab group 30 days after transplantation. | Wen et al. (2020), Non-randomized |
| OKT3 (muromonab)              | CyA (CYP3A)                   | 17 = OKT3, 16 = controls | - on days 1 and 3, CyA trough concentration did not differ but it was significantly higher in OKT3-group at day 5 as compared to control ($p<0.0001$). - on days 7 and 10, CyA trough level did not differ again | Tran et al. (2016), Case-control study |
| Adalimumab                    | duloxetine (CYP1A2 and 2D6)   | 22-years-old woman | - adalimumab was initiated for a refractory psoriasis but the peripheral neuropathy became unbearable leading to double the duloxetine’s dosage while she had a long-standing treatment by duloxetine and pregabalin, - authors did not suggest any interaction’s mechanism but it could be possible that the decrease of TNF-α by adalimumab led to a lift of the inhibition of CYPs, - no apparent interaction with pregabalin, which is eliminate by renal way | Lee et al. (2017), Case report |
| Infliximab                    | verapamil (CYP3A4, 1A2, 2C8, 2C9 and 2C19) | 12 = RA with infliximab, 8 = RA controls, 12 = healthy controls | - serum CRP and IL-6 concentrations were significantly greater in RA patients who were on nonbiologic antirheumatic therapy compared with controls ($p<0.001$ and $p<0.0001$, respectively). - CRP and IL-6 concentrations were not significantly different between RA patients taking infliximab and control subjects, - difference in RA patients who were on nonbiologic treatment in all PK parameters of verapamil, but it did not reach statistical significance but no difference between controls and RA patients who were taking infliximab, - infliximab did not show overall superiority to placebo on depressive symptom outcome | Davis et al. (2018), Case-control study |
| Infliximab                    | antidepressants               | 30 = infliximab, 30 = placebo | | Wollmann et al. (2017), RCT |
| Secukinumab                   | midazolam (CYP3A)            | 24 = Psoriasis Area Severity Index (PASI) score $>12$ taking secukinumab | - secukinumab treat the immune-mediated disease by neutralizing the underlying inflammation and tissue destruction, - patients with PASI score $>12$ taking secukinumab, a decreased in IL-6 and CRP levels were observed after the start of treatment, - any change was seen in the PK parameters of midazolam before and after the administration of secukinumab, - PK parameters of midazolam in patients with psoriasis (study subjects) were close to those in found in healthy subjects in a previous study | Sifontis et al. (2002), Non-randomized |
TABLE 14 | (Continued) Impact of therapies with anti-TNF-α and -mabs on CYP substrates, explained totally or partially by modulation of CYP activity.

| Inflammation characterized by | Victim drugs (CYPs concerned) | Number of subjects | Potential effect of interaction | References and design |
|-------------------------------|--------------------------------|--------------------|--------------------------------|----------------------|
| risankizumab                 | caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19) and metoprolol (CYP2D6) | 21                 | - risankizumab is an antibody that acts against IL-23 and it is involved in immune and inflammatory response thus, risankizumab inhibits its cells signalling pathway and the release of pro-inflammatory cytokines, - metabolic activity of CYP1A2, 2C9, 2C19, 2D6 and 3A4 were assessed before and 12 weeks after onset of treatment and any differences were observed, - authors conclude that treatment with risankizumab is not expected to cause CYP-mediated drug interactions | Vasquez and Pollak (1997), Non-randomized |
| tocilizumab                  | simvastatin (CYP3A)            | 12                 | - exposure to simvastatin was significantly reduced by approximately half at 1 and 5 weeks after tocilizumab infusion | Bruin et al. (2019), Randomized |
| sirukumab                    | midazolam (CYP3A), omeprazole (CYP2C19), warfarin (CYP2C9), caffeine (CYP1A2) | 12                 | - administration of probe drugs 1 week before and 1, 3 and 6 weeks after sirukumab administration, - AUC of midazolam, omeprazole and S-warfarin decreased and those of caffeine increased as compared with those before sirukumab administration, - it was not because it is a CYP inducers, but because the inhibition by inflammation may be reversed by its IL-6 antagonism, - for CYP1A2, this result suggests that inflammation induce its metabolic activity, - authors suggest that, according to literature, IL-6 may have a blijkspic impact on CYP1A2 activity depending on the IL-6 concentration, with an induction observed with low level of IL-6 and | Khatri et al. (2019), Non-randomized |
| dupilimumab                  | midazolam (CYP3A), omeprazole (CYP2C19), warfarin (CYP2C9), caffeine (CYP1A2) and metoprolol (CYP2D6) | 13                 | - no impact of blockade of IL-4 and IL-13 signalling on the metabolic activity of CYP3A, 2C9, 2C9, 1A2 and 2D6 | Mühbacher et al. (2021), Non-randomized |
| biological disease-modifying antirheumatic drugs | 4β-hydroxycholesterol (4βOHC) (CYP3A) | 31 = TNF-α inhibitor, 5 = IL-6 inhibitor, 5 = B-cells inhibitors, 52 = controls | - levels did not change after the onset of any of the three treatments, - a trend was observed that lowest baseline 4βOHC levels (higher inhibition of CYP3A4 metabolic activity) showed highest relative increase in at follow-up and thus a highest regain in metabolic activity of CYP3A4 after initiation of treatment, - authors suggest that the absence of variation in 4βOHC levels in this study could be explained by the low level of inflammation in these patients because 4βOHC level in the study population at baseline was only 30% lower than in control groups | Girardin et al. (2012), Cohort study and case-control study |
| TNF-α inhibitor              | 4βOHC (CYP3A)                  | 31                 | - CRP values were lower than before 3 months treatment, but the difference was not statistically significant (p > 0.2) and 4βOHC levels were not significantly affected (p > 0.9) by the initiation of treatment, - significant negative correlations were observed between 4βOHC and IL-1ra and IL-6 (r = -0.410, p = 0.022) and CXCL8 (r = -0.403, p = 0.023) | Chladek et al. (1999), Cohort study Same subject as in Girardin et al. (2012) |

(Continued on following page)
A minority of studies have evaluated the impact of inflammation on CYP substrates, explained totally or partially by modulation of CYP activity. Inflammation factors as covariates, such as biomarkers of renal or liver function (Stanke-Labesque et al., 2020).

Additionally, inflammation may have a different impact on CYPs activities depending on their baseline activity and on genotypic and environmental factors, such as concomitant treatments. Indeed, inflammation further increased the perampanel concentration/dose (C/D) ratio in patients not treated with drug inducers (Yamamoto et al., 2018). Voriconazole is also metabolized by highly polymorphic CYPs and inflammatory marker levels have a differential impact on voriconazole trough concentration whether patients are extensive, intermediate or ultra-rapid metabolized for CYP2C19 (Veringa et al., 2017). Moreover, a recent meta-analysis showed that voriconazole trough concentrations were independently influenced by both CYP2C19 and CYP3A4 genotype, considered individually or by a combined genetic score, in addition to CRP levels (Bolcato et al., 2021). In contrast, another cohort study showed that voriconazole overdoses were significantly associated with elevated CRP levels (>96 mg/L) but that CYP2C19 and CYP3A4 genotype, considered alone or combined in a genetic score, were not significantly different between overdose and non-overdose patients (Gautier-Veyret et al., 2019). Therefore, inflammation and pharmacogenomics may mutually minimize their reciprocal influence on CYP phenotype. Indeed, genotype did not predict correctly the phenotype in patients with inflammatory disease and the effect of inflammation was not as important as expected in CYP variants carriers (Helsby et al., 2008; Goktas et al., 2015; Burns et al., 2014; O'Neil et al., 2000; Williams et al., 2000; ). Consequently, inflammation could induce dynamic phenoconversion, characterized by dynamic phenotype-genotype mismatch, and studies examining the impact of inflammation on CYPs should assess CYP genotypes and phenotypes as covariates. It should however be pointed out that most of the included studies did not take into account routine treatment given to treat the diseases themselves.

Predictive models based on known interactions between molecular, environmental and lifestyle data by computational algorithm are increasingly developed to support the decision to individualize treatment (Iriart, 2019). Simulation of the
concentration-time profiles of a drug and its metabolite(s) and concomitant estimation of PK parameters using dynamic physiologically based pharmacokinetic (PBPK) models allow prediction of plasma concentration curves (Sager et al., 2015). There are increasing developments in regulatory guidelines (Sager et al., 2015). Inflammatory disease is an example of a special population and numerous PBPK models have been developed and validated to predict IL-6 mediated drug-disease (Machavaram et al., 2013; Xu et al., 2015; Jiang et al., 2016; Radke et al., 2017; Xu et al., 2018; Machavaram et al., 2019).

While IL-6 appears to be the key element in modulating CYP activities during inflammation, a recent study developed a model that predicted the impact of systemic CRP levels on CYP3A4 and CYP2C19 activities (Simon et al., 2021). Optimal drug use leads to takes into account the contribution of covariates to predict the dose needed to achieve a target concentration and thus reduce the inter- and intra-individual variability in drug response (Darwich et al., 2021).

This review focuses on CYP regulation, but other mechanisms, such as enzymes and transporters, involved in drug absorption, distribution, metabolism and elimination may be involved in changes in drugs PK during inflammatory states, although they are less studied. Studies described changes in plasma protein binding and renal excretion during inflammation that could affect CYP substrates metabolism (Gorski et al., 2000; Hefner et al., 2015; Helland et al., 2018). Plasma protein binding may influence total clearance for low-extraction drugs but not unbound clearance and may or may not influence half-life, depending on clearance and volume of distribution (Boffito et al., 2021). The unbound concentration and not the total concentration must be considered when assessing drug exposure to a highly protein-bound drug, otherwise there is a risk of misinterpretation of lopinavir overexposure (Boffito et al., 2021; Stanke-Labesque et al., 2021). For example, by taking into account plasma protein concentration, the authors concluded that CyA biotransformation by CYP3A may be downregulated by diabetes (Akhalghi et al., 2012). Decreased albumin concentration may increase the unbound concentration in diabetics, which should theoretically increase CyA metabolic clearance (Akhalghi et al., 2012). But the lower production of almost all metabolites has shown that the correct hypothesis is rather a reduced CYP activity (Akhalghi et al., 2012). In fact, CyA metabolites that involved amino acid 1 showed significantly lower dose-normalized AUC values in diabetic patients compared with nondiabetics suggesting that CYP3A4 metabolic activity was not decreased (Mendonza et al., 2008). Its dose-adjusted metabolite-parent concentration ratio was decreased in the diabetic groups, but no difference was found concerning doses and trough levels of CyA in a retrospective study (Wadhawan et al., 2000; Akhalghi et al., 2012).

Phase 2 drug metabolic enzymes appear to be affected in a cytokine-specific manner, as infection resulted in a significant downregulation of several genes encoding hepatic uridine 5’-diphospho-glucuronosyltransferases (UGT) (Stanke-Labesque et al., 2020). Pregnane X receptor (PXR) and constitutive androstane receptor (CAR), two nuclear receptors, are also cytokine dependent and mediate the expression of glutathione S-transferases (GST), UGTs and sulfuro-transferases (SULT) in humans (Wu and Lin, 2019). However, unlike voriconazole, posaconazole’s PK did not appear to be influenced by inflammation. This could be explained by a metabolism by phase 2 enzymes mainly (Märtson et al., 2019). Literature reviews on physiological changes related to drug PK and PD during inflammation may be useful to determine what investigations are needed to complement the data in the literature, such as the impact of inflammation on P-gp and other drug transporters, as one study showed that an increase in bioavailability due to downregulation of P-gp could not be ruled out (Sanaee et al., 2011).

Moreover, hepatic transporters that belong to ATP-binding cassette (ABC) and solute carrier (SLC) transporters have been shown to be significantly reduced during inflammatory states in animal and in-vitro studies (Stanke-Labesque et al., 2020). For instance, animals studies have shown that mRNA levels of MRP, OATP or BSEP were decreased in mice during inflammation (Wu and Lin, 2019). NF-κB, a transcription factors involved in the mechanism of action of cytokines on metabolizing enzyme gene expression, is also known to regulate the expression of numerous ABC and SLC transporters, including ABCB1 in humans and MDR1, MRP, BCRP, OATP, NTCP in rats and mice (Wu and Lin, 2019).

Given all of the above, it should be acknowledged that our literature search has some limitations. First, the completeness of the search cannot be guaranteed as we only searched one database and only published articles. Second, there is inevitably heterogeneity between the studies selected due to the different methodologies employed and low comparability between the studies identified. In addition, the diversity of the sources of inflammation studied and assessment of the clinical impact severity limits the robustness and generalizability of the results. Interpretations should therefore be addressed with particular caution.

CONCLUSION

This systematic literature review shows that inflammation is a major contributing factor to CYP metabolic activity variations. The proportion of the drug cleared by CYP metabolism, the patient’s genotype and concomitant medications should also be taken into account.

Compelling evidence suggests that inflammation has a differential impact on the various CYP isoforms with a different magnitude. CYP3A and CYP2C19 are downregulated and inflammation has no impact on CYP2D6 activity. Regarding other main CYPs, the impact remains unclear and requires further investigation. Moreover, the effect of inflammation depends on its severity and the inflammatory markers released, even if this remains debated. Indeed, the origin of the inflammation may differ as well as the inflammatory mediators involved, possibly leading to different impact on CYP activities. The reason why some CYP metabolic activities were modulated in some diseases and not in others may be partly explained by this heterogeneity in inflammatory markers.
Nonetheless, some results are still debated such as the impact of vaccination and infection, and further investigations are required to well characterize the impact of inflammation on CYP activity.

CYP is a major source of interindividual variability, and it appears crucial to be able to predict their activity to individualize drug dosing and take into account the patient’s underlying pathophysiological conditions and the PK characteristics of the drug concerned. Measurement of inflammation induced CYP phenocconversion and the development of endogenous markers of CYP metabolism should enable the measurement of CYP activity variation due to disease progression and could have implications for personalized medicine and provide new opportunities.

To conclude, inflammatory conditions in patients are a major factor to be considered to predict variability in drug response and avoid efficacy or safety issue in clinical practice.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

CL participated in the manuscript conceptualization, experimental design, writing and data analysis. CFS, JAD and VR participated in the manuscript conceptualization, supervision, overall manuscript review and English review.

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As shown, the PK characteristics of the drug concerned. Measurement of inflammation induced CYP phenocconversion and the development of endogenous markers of CYP metabolism should enable the measurement of CYP activity variation due to disease progression and could have implications for personalized medicine and provide new opportunities.
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