Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is a severe acute respiratory syndrome with an underlying inflammatory state. We have previously demonstrated that acute inflammation modulates cytochromes P450 (CYPs) activity in an isoform-specific manner. We therefore hypothesized that COVID-19 might also impact CYP activity, and thus aimed to evaluate the impact of acute inflammation in the context of SARS-CoV-2 infection on the six main human CYPs activity. This prospective observational study was conducted in 28 patients hospitalized at the Geneva University Hospitals (Switzerland) with a diagnosis of moderate to severe COVID-19. They received the Geneva phenotyping cocktail orally during the first 72 hours of hospitalization and after 3 months. Capillary blood samples were collected 2 hours after cocktail administration to assess the metabolic ratios (MRs) of CYP1A2, 2B6, 2C9, 2C19, 2D6, and 3A. C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α) levels were also measured in blood. CYP1A2, CYP2C19, and CYP3A MRs decreased by 52.6% ($P = 0.0001$), 74.7% ($P = 0.0006$), and 22.8% ($P = 0.045$), respectively, in patients with COVID-19. CYP2B6 and CYP2C9 MRs increased by 101.1% ($P = 0.009$) and 55.8% ($P = 0.0006$), respectively. CYP2D6 MR variation did not reach statistical significance ($P = 0.072$). As expected, COVID-19 was a good acute inflammation model as mean serum levels of CRP, IL-6, and TNF-α were significantly ($P < 0.001$) higher during SARS-CoV-2 infection. CYP activity are modulated in an isoform-specific manner by SARS-CoV-2 infection. The pharmacokinetics of CYP substrates, whether used to treat the disease or as the usual treatment of patients, could be therefore clinically impacted.

**Study Highlights**

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**
- Genetic, physiological, and environmental factors lead to high interindividual/intraindividual variability in CYP activity. Inflammation can downregulate CYP activity through pre-transcriptional and post-transcriptional mechanisms.

**WHAT QUESTION DID THIS STUDY ADDRESS?**
- What is the impact of acute inflammation triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on the activity of the six major human CYP isoforms?

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**
- SARS-CoV-2 infection and subsequent inflammation have an isoform-specific impact on CYP activity, with different magnitudes. Patients with COVID-19 had lower activities of CYP1A2, CYP2C19, and CYP3A. In contrast, CYP2B6 and CYP2C9 activities increased during COVID-19, whereas CYP2D6 activity was unchanged. The isoform-specific impact of SARS-CoV-2 infection on CYP activity was similar to our previous study that evaluated the impact of acute inflammation (hip surgery), but with a different effect size.

**HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**
- Patients with moderate/severe COVID-19 frequently receive CYP substrates to treat the infection and their underlying comorbidities. Awareness of the impact of COVID-19 on drug pharmacokinetics may improve drugs' benefit/risk ratio.
INTRODUCTION

The coronavirus disease 2019 (COVID-19), so named by the World Health Organization (WHO), emerged in late December 2019. It was identified as being caused by a coronavirus, which is a single-stranded RNA virus, later entitled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1

COVID-19 presents as a respiratory infection with a broad spectrum of symptoms.1 A minority of patients will present a severe to critical disease that could lead to acute respiratory distress syndrome and multiple organ failure.2 The host inflammatory response has been hypothesized to play an important role in the severity of the disease, with, in severe cases of COVID-19, an uncontrolled response of the immune system with massive release of proinflammatory cytokines.3 This life-threatening response is characterized by high levels of cytokines and hyperactivation of immune cells, hence the proportionality found between markers of inflammation and disease severity.4 Indeed, elevated proinflammatory markers, including C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin (IL)-2, IL-4, IL-6, and IL-10 levels, are proportional to COVID-19 severity.3,5 Moreover, IL-6 and TNF-α were independent and significant predictors of disease severity and death.6 Similarly, CRP correlated with disease severity and appeared to be a good predictor of adverse outcomes.7 Studies suggest that CRP levels are an excellent biomarker of the presence and severity of COVID-19, with the advantages that CRP is routinely measured to assess inflammation in patients.3

The impact of the release of immunogenic proteins during COVID-19 on CYP activity has not yet been studied, but data on CYP regulation by inflammatory proteins are well described.8 Indeed, several in vitro and animal studies, as well as studies conducted in humans, report that inflammation modulates cytochromes P450 (CYPs) activities.9,10 Moreover, using a cocktail approach, we have recently demonstrated that inflammation has an isoform-specific impact on CYP and with a different velocity.11 The underlying mechanisms are thought to be pre-transcriptional and post-transcriptional, with a reduction in messenger RNA levels or inhibition of its translation into protein.10 Specifically, several case reports of theophylline and clozapine toxicity after the onset of respiratory tract infection are described in the literature.10,12–14 Authors suggested that the increase of clozapine and theophylline plasma concentrations were linked to CYP1A2 inhibition. Furthermore, pneumonia could inhibit CYP3A4 according to two case reports studying perampanel and risperidone pharmacokinetic parameters, respectively.15,16 Similarly, some authors have started to investigate the impact of COVID-19 on CYP substrates, and available results were reviewed.8 The plasma concentrations of some CYP3A substrates (lopinavir, darunavir, and direct oral anticoagulants) were indeed shown to be significantly higher in patients with COVID-19.17–20 Lopinavir concentrations were also associated with CRP and IL-6 levels as they decreased after tocilizumab administration in patients with COVID-19.18,21 Finally, clozapine toxicity symptoms and increased clozapine level were reported during COVID-19.22 These findings warrant further investigation, as patients with severe COVID-19 often have several comorbidities and treatments, and some drugs administered to patients with COVID-19 are CYP substrates.23,24 Thus, the probability that patients with COVID-19 received CYP substrates is high and these isoenzymes are known to have interindividual and intraindividual variability over a period of time, which are the consequences of the interplay between genetic, environmental, and physiological factors.15

We therefore sought to evaluate the effects of moderate to severe COVID-19 as a model of acute inflammation on the activity of the six major CYPs in patients hospitalized with SARS-CoV-2 infection, using a phenotyping cocktail approach. To our knowledge, this is the first time that the impact of COVID-19 has been assessed simultaneously on the six main human CYPs.

METHODS

Study protocol

This study assessed the impact of moderate to severe COVID-19 on the activities of the six main human CYPs, namely CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A, through a prospective open-label observational study. The regional research ethics committee of the canton of Geneva (CCER) approved the amendment to the study protocol (No. 2016-02232), and the study was registered with the US National Institutes of Health Clinical Trials Registry (NCT03262051). All patients gave written informed consent before the start of any study procedure. The principles of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice were followed.

Study population

Participants were recruited within the first 72 hours of hospitalization at the Geneva University Hospitals for COVID-19 over a period from October 30 to December 12, 2020. Inclusion and exclusion criteria are described in Table S1. World Health Organization (WHO) criteria were used to assess the severity of COVID-19.25 Comedications were systematically run through the Lexi-Interact drug interaction checker and the Geneva table of CYPs to identify CYP inhibitors and inducers.6,26 Patients receiving dexamethasone were not excluded because it is currently a standard of care for the management of hospitalized patients with COVID-19.27 To limit the inducing effect of dexamethasone on CYP3A activity, only patients who received dexamethasone 5 mg once daily up to two times were included.

The primary objective was to measure the variation in activity of the six major human CYPs during and 3 months after (defined as baseline) SARS-CoV-2 infection.

Genotyping of CYP2B6, CYP2C9, CYP2C19, and CYP2D6

The method used to genotype CYP2B6, CYP2C9, CYP2C19, and CYP2D6 has already been described in detail in the literature.28 Genetic profile information from genotyping (single-nucleotide variants) and copy number assay were translated using the same software as in our previous study conducted in patients who underwent elective hip surgery.29

Phenotyping

Phenotype assessment technique has been previously described.11 CYP activity and subsequent phenotypic classification were based on metabolic ratios (MRs), defined as the concentration of the metabolite divided by the concentration of substrate. These concentrations were assessed by a validated method using liquid chromatography–tandem mass spectrometry quantification.30–32 Based on their MRs for each CYP, patients were classified as poor metabolizers (PMs), normal metabolizers (NMs), and ultra-rapid metabolizers (UMs), as well as intermediate metabolizers for CYP2D6. Threshold values were the same as those already detailed in our previous cohort study.31
The MRs of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A were measured twice, i.e., during the first 72 hours of the patient's hospitalization and 3 months after. To assess the phenotype of each CYP of interest, probe substrates contained in the Geneva cocktail (caffeine 50 mg, CYP1A2; bupropion 20 mg, CYP2B6; flurbiprofen 10 mg, CYP2C9; omeprazole 10 mg, CYP2C19; dextromethorphan 10 mg, CYP2D6; midazolam 1 mg, CYP3A; fexofenadine 25 mg, P-glycoprotein) were orally administered and capillary blood samples were collected 2 hours later from a fasting patient, with dried blood spots using a previously validated sampling method. Phenotypic P-glycoprotein (P-gp) activity was not assessed because it requires an area under the curve (AUC) of fexofenadine blood concentration (two additional capillary blood samples required 3 and 6 hours later) and this was deemed inappropriate in the context of hospital overload during the second wave of SARS-CoV-2 infection. Dried blood spots were then stored at −20°C in a sealed plastic bag until analysis, as previously described. No mutual drug–drug interactions were observed in the Geneva cocktail. CYP2D6 was not modulated by bupropion because of the extremely low doses and time intervals used.

**Inflammatory markers levels**

Whole blood samples with lithium heparin and without additive were collected twice in the early morning, namely during the first 72 hours of patients’ hospitalization and 3 months later, respectively, to assess CRP, IL-6, and TNF-α levels. The analysis methodology is described in detail in our previous study.

**Data and statistical analysis**

A sample size of 16 subjects was required to detect > 30% reversal of CYP3A activity with 80% power and an α value of 5%. In terms of correlation of CYP function with IL-6 (and other proinflammatory markers), a sample size of 24 subjects was required to consider a coefficient of 0.55 as significant, with 80% power and an α value of 5%. The sample size of 24 subjects allows detection of a > 22% difference in CYP MRs between pairs, assuming that the standard deviation (SD) of the differences is 36% (literature estimate of MR standard deviation for CYP3A).

To prevent loss to follow-up, a sample size of 30 subjects was targeted. A P value < 0.05 was considered statistically significant, and IBM SPSS Statistics software version 25 (Chicago, IL) was used to perform all statistical analyses. Continuous variables were described as means ± SD and a paired t-test was used to determine the percentage difference in MRs and levels of inflammatory markers before and after COVID-19. After testing for normality by the Kolmogorov-Smirnov test and finding that the normality assumption was generally not met, a nonparametric Spearman correlation test was applied. Spearman correlations were assessed between different variables such as variation (delta) in inflammatory markers levels and CYP MRs, body mass index (BMI), and age (continuous variable), and a t-test was applied between variation (delta) of CYP MRs and sex, dexamethasone use, COVID-19 severity classification (severe vs. moderate), or diabetic status (binary variables). Continuous variables were standardized. A multiple linear regression model was built to evaluate the inflammatory markers influencing the variation (delta) in CYP activity (dependent variables) observed during and after COVID-19 by controlling the other predictors put in the model. The independence between all the variables was verified using a collinearity test.

**RESULTS**

**Demographic**

Thirty subjects were included for the first part of the study, but two withdrew their consent for the second part of the study (3 months later) and were thus excluded. The summary of patients’ demographics and clinical characteristics is presented in Table S2. Hospitalization and inclusion after symptoms onset were based on 27 patients, as one patient was hospitalized on the day of incidental discovery of infection.

**Proinflammatory markers**

The effect of SARS-CoV-2 infection on inflammatory markers (CRP, IL-6, and TNF-α) serum levels are shown in Figure 1 and Table 1.

**CYP activity during and after SARS-CoV-2 infection**

Table 2 shows the activities of the 6 CYPs of interest during (acute inflammation) and 3 months after (baseline levels) SARS-CoV-2 infection. CYP1A2, CYP2C19, and CYP3A MRs decreased by 52.6% (P = 0.0001), 74.7% (P = 0.0006), and 22.8% (P = 0.045), respectively, during SARS-CoV-2 infection. Inversely, CYP2B6 and CYP2C9 MRs increased by 101.1% (P = 0.009) and 55.8% (P = 0.0006), respectively, while the 35.2% increase of CYP2D6 MRs did not reach statistical significance (P = 0.072).

**Phenoconversion**

Table S3 shows the patients’ genotype with allele frequencies and predicted phenotype from genotype for each CYP. The predicted phenotype matched the measured phenotype 3 months after COVID-19 in 82.1%, 64.3%, and 75.0% of patients for CYP2B6, 2C19, and 2D6, respectively. For 82.1% of patients, the predicted phenotype for CYP2C9 did not reflect the measured phenotype 3 months after SARS-CoV-2 infection. Almost all (78.6%) of them had an accelerated CYP2C9 measured phenotype compared with the predicted phenotype. For CYP2C19, 179% of patients had a decreased measured phenotype 3 months after COVID-19 compared with the predicted phenotype.

A phenotypic switch from NM to PM or from UM to NM was observed in 71%, 46%, and 43% of subjects for CYP1A2, CYP2C19, and CYP3A, respectively, during COVID-19 (Figure 2a–e). Fifty-four percent of subjects were CYP2C19 PMs 3 months after COVID-19 (Figure 2b). Phenoconversion from PM to NM or from NM to UM was observed in 36% and 29% of subjects for CYP2B6 and CYP2C9, respectively (Figure 2d,e). Twenty out of the 28 included patients had no CYP2C9 phenoconversion, but 19 of them were CYP2C9 UMs 3 months after COVID-19 (Figure 2e). Concerning CYP2D6, no change of phenotypic category was observed in 79% of subjects (Figure 2f).

**Variables that influenced the change in CYP activity**

Table 3 shows Spearman correlations performed on the variation of the MRs of CYP isoform during and 3 months after COVID-19, and different factors, such as variation of proinflammatory markers, BMI, sex, age, COVID-19 severity, diabetic status, or dexamethasone intake. No correction for multiple testing was performed. An increased level of CRP was associated with a more marked inhibition of CYP3A, and the older the patients, the more CYP2C19 and CYP2B6 were inhibited (significant negative association), and CYP2C19 activity was higher in women (significant positive association).

A multiple linear regression model was built to assess factors associated with variation of CYP activity while controlling the other predictors put in the model, such as variation of proinflammatory effect of SARS-CoV-2 infection on inflammatory markers (CRP, IL-6, and TNF-α) serum levels are shown in Figure 1 and Table 1.

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markers, BMI, sex, age, COVID-19 severity, diabetic status, or dexamethasone intake. Independence was tested by a collinearity test (variation inflation factor), and all the covariables were independent of each other. However, the focus was on variation in proinflammatory markers in relation to variation in CYP activity (Table 4).

The model was a significant predictor of variations in CYP1A2 and CYP2D6 MRs but not for CYP2B6, CYP2C9, CYP2C19, and CYP3A4, as shown in Table S4. The same associations between variation in CRP, IL-6, and TNF-α levels and CYP MRs were not found in the multiple linear regression model compared

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**Figure 1** Serum levels of the three inflammatory markers (a) CRP, (b) IL-6, and (c) TNF-α during and 3 months after SARS-CoV-2 infection (n = 28). The boundary of the box closest to zero indicates the 25th percentile, the black line within the box marks the median, the cross within the box marks the mean, and the boundary of the box farthest from zero indicates the 75th percentile. Whiskers above and below the box indicate the 10th and 90th percentiles. Points above and below the whiskers indicate outliers. CRP, C-reactive protein; IL-6, interleukin 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF-α, tumor necrosis factor-α. [Colour figure can be viewed at wileyonlinelibrary.com]

**Table 1** Mean MRs ± SD of the three inflammatory markers

| Inflammatory markers | Serum levels units | During COVID-19 | After COVID-19 | P value |
|----------------------|--------------------|-----------------|----------------|---------|
| CRP                  | mg/L               | 91.7 ± 44.6     | 2.4 ± 1.9      | 4.02 × 10^{-11} |
| IL-6                 | ng/mL              | 9.72 ± 11.77    | 1.14 ± 1.58    | 7.86 × 10^{-4}   |
| TNF-α                | ng/mL              | 4.95 ± 1.96     | 2.94 ± 1.16    | 8.20 × 10^{-7}   |

Mean MRs ± SD of the three inflammatory markers measured during and 3 months after SARS-CoV-2 infection (n = 28) (P < 0.05 is significant). COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IL-6, interleukin 6; MRs, metabolic ratios; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF-α, tumor necrosis factor-α.
with Spearman correlations. Indeed, variation in CRP levels was associated with variation in CYP3A MRs, IL-6 levels with CYP1A2 and CYP2C9, and TNF-α levels with CYP2D6. This could be explained by the fact that each proinflammatory marker was controlled by the other two, and the release of CRP and TNF-α is initiated by IL-6. The variation in TNF-α level was removed because the difference was small between the COVID-19 stage and 3 months later, and this variation was almost within the expected ranges of variability. The new model thus significantly predicted the variation in CYP2C9 and CYP3A activity, as shown in Table S4. These coefficients of variation and P value associated with the change in serum CRP and IL-6 levels were not modified in this model compared with the first model integrating TNF-α change.

Therefore, the change in activity of some CYPs observed during SARS-CoV-2 infection correlated with several variables, such as variation in CRP levels (CYP3A), IL-6 levels (CYP1A2 and CYP2C9), and TNF-α levels (CYP2D6), sex (CYP2C19), and age (CYP2C19 and CYP2B6). BMI, diabetic status, dexamethasone intake, and COVID-19 severity were not correlated with CYP variations observed during SARS-CoV-2 infection.

Smoking status and initiation of CYP modulator treatments between the beginning and end of the study were not taken into account because they involved only one and three patients, respectively. Moreover, only CYP3A and CYP2C19 inhibitors were initiated and these CYPs were already inhibited during SARS-CoV-2 infection; thus, the only consequence would have been an offset of the inhibitory effect of inflammation on CYP3A and CYP2C19 activities during SARS-CoV-2 infection, which was not observed.

**DISCUSSION**

We have demonstrated that SARS-CoV-2 infection has an isoform-specific impact on the activity of the six main human CYPs, with different effect and magnitude. To our knowledge, this is the first time that a cocktail approach was used to study CYP activity in COVID-19.

To date, only five studies and one case report have reported the impact of SARS-CoV-2 infection on CYP substrates, but not on probe drugs.17–22 Indeed, one case report described the onset of symptoms of clozapine toxicity associated to a clozapine level that increased after COVID-19.22 In addition, lopinavir/ritonavir as well as darunavir, all of which are CYP3A substrates, have been used as a treatment for SARS-CoV-2 infection. Their trough concentrations were significantly higher and their clearances lower in patients with COVID-19 compared with patients with HIV.17,18,20 Lopinavir plasma concentrations were associated with CRP levels in patients with COVID-19 and were significantly lower when tocilizumab was administered beforehand.18,21 Finally, direct oral anticoagulants are also CYP3A substrates and an alarming increase in their plasma levels was observed, as compared with prehospitalization levels.19 However, a possible role of concomitant drugs or disease-related organ dysfunction cannot be excluded.19

The isoform-specific impact of SARS-CoV-2 infection on CYP activity was similar to our previous study that evaluated the impact of another acute inflammation model (hip surgery).11 However, the effect size was higher for CYP2C19 and lower for CYP3A, CYP2B6, and CYP2C9. It was similar for CYP1A2 and CYP2D6. CYP2C19 was the most downregulated CYP, with a decrease by 75% during SARS-CoV-2 infection, and the decreased activity was inversely correlated with IL-6 and CRP levels. In our previous cohort study, CYP2C19 activity decreased by 57% and was inversely correlated with CRP levels.11 This is in accordance with previous publications that demonstrated a decrease of CYP2C19 activity during an inflammatory condition, and negative correlations with IL-6 and TNF-α.35,36 Moreover, the ratio of clopidogrel active metabolite (bioactivated by CYP2C19) to clopidogrel has been shown to be 48-fold higher in healthy subjects than in critically ill patients, and platelet aggregation was significantly higher in patients with elevated CRP levels.37,38

We could not demonstrate correlation between the variations of CYP2C19 MR and any of the proinflammatory markers. Difference in the kinetics of these variables might explain the absence of correlation, due to an expected time lag between elevation of proinflammatory markers and CYP downregulation. Furthermore, proinflammatory markers were measured during the first 72 hours of hospitalization in patients with COVID-19 and so a discordance in proinflammatory marker levels could exist among our included patients because they were not hospitalized at exactly the same time after disease onset, or they were not included exactly

**Table 2 Mean MRs ± SD of the six CYP isoforms**

| Isoforms | MRs parameters (Mean ± SD) | During SARS-CoV-2 infection | 3 months after SARS-CoV-2 infection | P value |
|----------|-----------------------------|-----------------------------|-------------------------------------|---------|
| CYP1A2   | (paraxantine) / (caffeine)  | 0.199 ± 0.081               | 0.420 ± 0.258                      | 0.0001  |
| CYP2C19  | (OH-omeprazole) / (omeprazole) | 0.148 ± 0.129             | 0.586 ± 0.671                      | 0.0006  |
| CYP3A    | (OH-midazolam) / (midazolam) | 0.428 ± 0.289             | 0.550 ± 0.240                      | 0.045   |
| CYP2B6   | (OH-bupropion) / (bupropion) | 2.263 ± 2.502             | 1.324 ± 0.844                      | 0.009   |
| CYP2C9   | (OH-flurbiprofen) / (flurbiprofen) | 0.120 ± 0.062            | 0.077 ± 0.031                      | 0.0006  |
| CYP2D6   | (dextrophan) / (dextrorphan)  | 3.010 ± 2.381             | 2.226 ± 2.078                      | 0.072   |

Mean MRs ± SD of the six CYP isoforms during and 3 months after SARS-CoV-2 infection (n = 28) (P < 0.05 is significant).

CYP, cytochrome P450; MRs, metabolic ratios; OH, hydroxy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
at the same time after the beginning of their hospitalization. It is particularly important to note that phenoconversion was observed in 100% of patients who were not PMs at baseline. Indeed, the phenoconversion observed in slightly less than half of the subjects, as shown in Figure 2b, can be explained by the fact that half of the individuals carried alleles associated with decreased CYP2C19 activity (Table S3). Moreover, out of the three NM patients predicted on the basis of genotype who had a PM phenotype 3 months after SARS-CoV-2 infection, one was started on esomeprazole, a well-known CYP2C19 inhibitor. We cannot exclude that the other two took CYP2C19 inhibitors without informing us.

We found that CYP1A2 was the second-most downregulated CYP with a decrease of 53% during SARS-CoV-2 infection, with inverse correlation with IL-6 and CRP levels. The same magnitude and correlations were found for CYP1A2 in hip surgery patients. These results are in agreement with previous published studies, since many case reports have described increased clozapine and theophylline toxicity or plasma concentrations during inflammatory conditions, such as infection or elevated levels of CRP. IL-6 but not TNF-α levels have been inversely correlated with CYP1A2 activity in 16 patients with congestive heart failure. Recently, a case report of clozapine toxicity with increased level during

Figure 2 Percentage of patients (n = 28) with CYP phenotypic switch between 3 months after (baseline) and during SARS-CoV-2 infection: (a) CYP1A2, (b) CYP2C19, (c) CYP3A, (d) CYP2B6, (e) CYP2C9, and (f) CYP2D6. CYP, cytochrome P450; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. [Colour figure can be viewed at wileyonlinelibrary.com]
Table 3  Correlation between change in CYPs MRs and change in serum pro-inflammatory markers levels

|               | Δ CYP1A2 | Δ CYP1C9 | Δ CYP3A | Δ CYP2B6 | Δ CYP2C9 | Δ CYP2D6 |
|---------------|----------|----------|---------|----------|----------|----------|
| Δ CRP         | r = -0.305 (P = 0.115) | r = -0.090 (P = 0.648) | r = -0.516 (P = 0.005) | r = -0.076 (P = 0.700) | r = -0.183 (P = 0.352) | r = -0.084 (P = 0.672) |
| Δ IL-6        | r = -0.068 (P = 0.730) | r = 0.178 (P = 0.364) | r = 0.063 (P = 0.751) | r = -0.117 (P = 0.554) | r = 0.225 (P = 0.250) | r = 0.092 (P = 0.643) |
| Δ TNF-α       | r = 0.005 (P = 0.980) | r = -0.139 (P = 0.480) | r = -0.137 (P = 0.486) | r = -0.143 (P = 0.467) | r = 0.093 (P = 0.638) | r = 0.449 (P = 0.017) |
| Sex           | t = 1.683 (P = 0.104) | t = 2.940 (P = 0.007) | t = -0.920 (P = 0.366) | t = 1.211 (P = 0.237) | t = -1.060 (P = 0.299) | t = -0.119 (P = 0.906) |
| Age           | r = -0.109 (P = 0.581) | r = -0.487 (P = 0.009) | r = -0.037 (P = 0.852) | r = -0.493 (P = 0.008) | r = -0.018 (P = 0.928) | r = 0.039 (P = 0.842) |
| BMI           | r = 0.060 (P = 0.760) | r = -0.192 (P = 0.327) | r = -0.141 (P = 0.473) | r = 0.201 (P = 0.306) | r = -0.067 (P = 0.736) | r = -0.001 (P = 0.997) |
| COVID-19 severity (moderate vs. severe) | t = -0.716 (P = 0.480) | t = 0.460 (P = 0.649) | t = 0.281 (P = 0.781) | t = 1.819 (P = 0.080) | t = -0.811 (P = 0.475) | t = -1.171 (P = 0.252) |
| Diabetic status | t = 1.006 (P = 0.324) | t = 8.585 (P = 0.399) | t = -0.375 (P = 0.710) | t = 2.112 (P = 0.086) | t = -0.261 (P = 0.796) | t = 0.167 (P = 0.696) |
| Dexamethasone intake | NA | NA | t = -0.252 (P = 0.803) | NA | NA | NA |

Correlation (Spearman) between change in MRs (delta) of the six CYP isoforms and change (delta) is serum IL-6, TNF-α and CRP levels during and 3 months after SARS-CoV-2 infection in the 28 subjects (P < 0.05 is significant). CRP, C-reactive protein; CYP, cytochrome P450; IL-6, interleukin 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNFα, tumor necrosis factor-α.

Table 4  Linear regression model of the difference in CYPs MRs

|               | Δ CYP1A2 | Δ CYP1C9 | Δ CYP3A | Δ CYP2B6 | Δ CYP2C9 | Δ CYP2D6 |
|---------------|----------|----------|---------|----------|----------|----------|
| Δ CRP         | -0.342 (SE = 0.174) | -0.242 (SE = 0.191) | -0.468 (SE = 0.182) | -0.031 (SE = 0.200) | -0.151 (SE = 0.181) | -0.302 (SE = 0.170) |
| Δ IL-6        | -0.439 (SE = 0.178) | 0.229 (SE = 0.196) | 0.084 (SE = 0.186) | -0.068 (SE = 0.205) | 0.443 (SE = 0.185) | 0.074 (SE = 0.175) |
| Δ TNF-α       | 0.060 (SE = 0.180) | -0.204 (SE = 0.198) | 0.008 (SE = 0.188) | -0.210 (SE = 0.207) | 0.057 (SE = 0.187) | 0.496 (SE = 0.176) |

Standardized variables in the linear regression model and association with the difference in metabolic activities of the six CYP isoforms during and 3 months after SARS-CoV-2 infection in the 28 subjects (P < 0.05 is significant). CRP, C-reactive protein; CYP, cytochrome P450; IL-6, interleukin 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNFα, tumor necrosis factor-α.

SARS-CoV-2 infection was described.22 The impact of inflammation appears to be linked to disease severity, as metabolic status of caffeine did not change in HIV-infected asymptomatic patients but decreased in patients with AIDS (with acute illnesses).39 We found a phenotypic switch in 71% of included patients.

The decrease in CYP3A activity by 23% during SARS-CoV-2 infection was of smaller magnitude than in hip surgery patients (60% decrease).11 This may be due in part to the use of dexamethasone, which is known to be a weak inducer of CYP3A, even if no correlation was found. Moreover, one patient started amiodipine between the end of his hospitalization and 3 months later (baseline). This may explain reduced activity at baseline and an apparently reduced downregulation of CYP3A activity by inflammation, as amiodipine is considered a weak CYP3A4 inhibitor.40 Furthermore, in an acute inflammation surgery model, we previously showed that the maximal decrease of CYP3A activity occurred after 3 days, and therefore maximal inhibition of CYP3A might not have been reached at the time of measurement.11 Still, 43% of patients experienced a phenocconversion during SARS-CoV-2 infection. We found an inverse correlation with CRP levels, which is in accordance with a previous study in proportion to disease severity.11 Lopinavir trough concentrations also significantly increased and were positively correlated with CRP levels in patients with COVID-19.18,21

We showed that CYP2B6 activity increased by 100% during SARS-CoV-2 infection. We found an inverse correlation with CRP levels, which is in accordance with a previous study in proportion to disease severity.41 Lopinavir trough concentrations also significantly increased and were positively correlated with CRP levels in patients with COVID-19.18,21

In a previous study, we found a phenotypic switch in 71% of included patients. We found a phenotypic switch in 71% of included patients.
receptor may be acting as a regulation factor as a consequence of cortisol secretion in patients with COVID-19 and stress may thus explain the observed CYP2B6 induction. A cohort study indeed showed that median cortisol concentration in patients with COVID-19 was significantly higher than controls ($P < 0.0001$) and that the patients with COVID-19 had a marked acute cortisol stress response. Therefore, cortisol might be a marker of disease severity.

CYP2C9 activity increased by 56% in SARS-CoV-2 infection, while it increased by 79% after surgery. This could be of clinical relevance since phenocrvonsation was demonstrated in 89% of patients who were not UMs at baseline. Surprisingly 19 out of 28 patients in the cohort were UMs 3 months after SARS-CoV-2 infection while no genetic variant is currently known to increase CYP2C9 activity and there was no CYP2C9 inducer in the medications. The persistent induced activity of CYP2C9 could be explained either by an unidentified environmental factor or by the existence of as yet undescribed genetic variants. Moreover, the validated cutoff values of the Geneva cocktail for CYP2C9 are based on a study in which volunteers were simultaneously administered rifampin and fluconazole, a CYP2C9 inducer and a CYP2C9 inhibitor, respectively, which are not specific to CYP2C9. Indeed, a very low correlation (17.9%) between the predicted phenotype and the measured phenotype at baseline level was found in this cohort. It is gradually recognized that SARS-CoV-2 can induce long-term complications after recovery from the acute effects of infection, even if these long-term health consequences remain largely unclear. According to the National Institute for Health and Care Excellence (NICE), long COVID-19 is a range of symptoms that can last weeks or months after first being infected with the virus. In the United Kingdom, around one in five people who tested positive for COVID-19 had symptoms that lasted for 5 weeks or longer, and one in ten people had symptoms that lasted for 12 weeks or longer. One recent study showed that only 12.6% of patients were completely free of any COVID-19 symptoms after 60 days and that 55% still had three or more symptoms. Another study with a longer follow-up period showed that 24.1% of patients still had at least one symptom after 90 days, this figure reaching 40.6% in those with most severe initial acute disease. We hypothesize that CYP2C9 activity levels measured 3 months after infection could be associated with long COVID-19 metabolic disturbances, yet to be identified. Indeed, ~30% of our included patients still described long-term effects of COVID-19 at 3 months. It would thus be of interest to reassess CYP activity in our cohort of patients with COVID-19 with a much longer delay to further support this hypothesis. Indeed, it is estimated that recovery of CYP activity after discontinuation of inducers can be achieved in 14 days, which is longer than after discontinuation of mechanism-based (10 days) or competitive inhibitors (which depend on their elimination half-life).

Finally, COVID-19 had no significant impact on CYP2D6 activity, as already observed in surgery-induced acute inflammation. A recent cohort study did not find any correlation between CRP and hydroxychloroquine plasma concentration in patients with COVID-19, treated or not with tocilizumab. CYP2D6 activity was not influenced by diabetic status either. However, conflicting results have been published in patients infected with HIV. This observation could be explained by the fact that CYP2D6 has a high intradividual variability, and dextromethorphan MR can vary up to 50% within healthy subjects. The significant Spearman correlation and coefficient found between the change in TNF-α level and the change in CYP2D6 MR between SARS-CoV-2 infection and situation 3 months later should be taken with caution. Indeed, the change in TNF-α level was small and within the range of variability.

A longitudinal study in patients with COVID-19 previously showed that TNF-α levels peaked 3 to 6 days after disease onset and no difference in their levels was observed between the mild and severe groups. IL-6 reached its serum peak between days 7 and 9 after disease onset in patients with mild COVID-19, whereas the reduction in serum IL-6 levels in severe patients began 16 days after disease onset. In another longitudinal analysis of hospitalized patients with COVID-19, median TNF-α and IL-6 levels in noncritically ill patients were 7.3 pg/mL and 5.0 pg/mL, respectively, during the first 3 days of hospitalization. These figures are comparable to the mean levels found in our cohort, where the mean concentrations were 9.72 and 4.95 ng/mL, respectively. In a retrospective study, mean CRP levels at admission were 16.76, 54.15, and 105.00 mg/L in the moderate, severe, and critical groups, respectively. These results are comparable to the mean CRP level of 91.7 mg/L found in the first 72 hours of admission in our study.

We thus have demonstrated that COVID-19 has an impact on CYP activity in an isofom-specific manner (inhibition or induction, and magnitude). The magnitude of the effects found on CYP1A2, CYP2C19, CYP3A, CYP2B6, and CYP2C9 activities might be of clinical relevance, in particular in polymorbid and polymedicated patients with COVID-19.

Our study has some limitations. First, the sample size was relatively small and confirmation of our multiple linear regression model findings in an additional and/or broader sample is needed, allowing for possible adjustment with other covariables. In addition, a correlation between COVID-19 and variation in CYPs’ activity was found, but further investigations are needed to corroborate it. In particular, the patients included had different health status, such as hypertension, diabetes, dyslipidemia, or none. Finally, the duration of follow-up was of only 3 months and there is no guarantee that CYP activity in included patients had returned to their initial levels, in light of considerations about the potential long-term effects of COVID-19. A study with a longer follow-up time may provide answers and should include the statement of symptoms of long COVID-19.

To conclude, our results suggest that SARS-CoV-2 infection and the resulting acute inflammation have a large impact on the activity of six key CYPs in an isofom-specific manner. These effects could be prolonged for certain isofoms. Our findings may help manage relevant drug efficacy and safety issues in the context of COVID-19 through the impact on the PK of drugs that are substrates of these major drug-metabolizing enzymes, whether used to treat acute disease or as routine patient therapy.
SUPPORING INFORMATION
Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

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CONFLICT OF INTEREST
The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
C.L., J.T., and C.F.S. wrote the manuscript. C.L., J.T., Y.G., F.C., V.R., Y.D., J.A.D., J.-L.R., and C.F.S. designed the research. C.L. performed research. C.L., J.T., F.C., and C.F.S. analyzed the data. C.L., Y.G., and Y.D. contributed new reagents/analytical tools.

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