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Review

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Recommendations on the use of azole antifungals in hematology-oncology patients

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ABSTRACT

The administration of antifungals for therapeutic and, especially, prophylactic purposes is virtually a constant in patients requiring hematology-oncology treatment. Any attempt to prevent or treat *Aspergillus* or *Mucor* infections requires the administration of some drugs in the azole group, which include voriconazole, posaconazole and isavuconazole, noted for their activity against these pathogens. One very relevant aspect is the potential risk of interaction when associated with one of the antineoplastic drugs used to treat hematologic tumors, with serious complications. In this regard, acalabrutinib, bortezomib, bosutinib, carfilzomib, cyclophosphamide, cyclosporine A, dasatinib, duvelisib, gilteritinib, glasdegib, ibrutinib, imatinib, nilotinib, ponatinib, prednisone, ruxolitinib, tacrolimus, all-transretinoic acid, arsenic trioxide, venetoclax, or any of the vinca alkaloids, are very clear examples of risk, in some cases because their clearance is reduced and in others because of increased risk of QTc prolongation, which is particularly evident when the drug of choice is voriconazole or posaconazole.

Keywords: Azoles, hematology patients, drug-drug interactions

Recomendaciones sobre el uso de antifúgicos azolicos en el paciente oncohematológico

RESUMEN

La administración de antifúngicos con fines terapéuticos y especialmente, profilácticos es casi un constante en el paciente que precisa tratamiento oncohematológico. El intento de evitar o de tratar infecciones por *Aspergillus* o por *Mucor* exige la administración de algunos fármacos pertenecientes al grupo de los azoles, entre los que destacan por su actividad frente a estos patógenos, voriconazol, posaconazol e isavuconazol. Un aspecto de gran importancia es el riesgo potencial de interacciones cuando se asocian a alguno de los fármacos antineoplásico utilizados en el tratamiento de los tumores hematológicos, dando lugar a graves complicaciones. En este sentido, acalabrutinib, bortezomid, bosutinib, carfizolid, ciclofosfamida, ciscloporina A, dasatinib, duvelisib, gilteritinib, glasdegib, ibrutinib, imatinib, nilotinib, ponatinib, prednisona, ruxolitinib, tacrolimus, trans-

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retinoico, trióxido de Arsenio, venetoclax, o cualquiera de los alcaloides de la vinca, representan ejemplos muy evidentes de riesgos en unos casos porque su aclaramiento resulta reducido, en otros porque que se potencia el riesgo de prolongación del QTc, especialmente evidentes cuando el fármaco elegido es voriconazol o posaconazol.

Palabras clave: Azoles, pacientes hematológicos, interacciones medicamentosas

PREAMBLE

The reduction in patient immunity resulting from the use of increasingly effective drugs in the treatment of serious diseases has led, inter alia, to an increase in the frequency and severity of invasive fungal infections. This circumstance is common in oncology patients, among whom hematology-oncology patients are a very special population as they commonly present with long-lasting neutropenia [1-5] Some genera of fungi are especially frequent in the genesis of invasive fungal infection. *Candida*, *Aspergillus*, *Scedosporium*, *Fusarium* and *Mucorales* are notable examples of pathogens with high mortality, both in general and in this type of patients: *Candida* exceeds 10% while the remaining pathogens, including *Aspergillus*, can exceed 50%. Given this characteristic, the use of antifungals with activity against this type of pathogens is essential for both the prophylaxis and treatment of this type of infectious disease.

Since their spectrum encompasses most of the above pathogens, and *Aspergillus* in particular, the azoles (itraconazole, voriconazole, posaconazole and isavuconazole) are the most notable antifungals used in this indication. The management of these drugs, whose most typical characteristics are detailed below, is complex in several areas, including the risk of interactions with other drugs due to the altered enzymatic activity of some CYP450 components, and also because of their capacity to prolong the QT interval. These two situations often pose a serious problem when the patient is treated with any of the more relevant hematology-oncology drugs. The authors therefore considered it appropriate to make the specific recommendations set out in this article.

CYP450 SYSTEM AND TRANSPORT PROTEINS

The origins of the pharmacokinetic interactions involving azoles lie in the capacity exhibited by these drugs to inhibit the activity of some of the CYP450 isoenzymes that also participate in their metabolism. In addition, some of the drugs are substrates of transport proteins, especially P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) which they are also capable of inhibiting. This suggests risks of interactions with other drugs that are substrates of these transport proteins. Table 1 describes the effects of the various azoles on the different CYP450 isoenzymes and transport proteins.

The CYP450 system is a group of enzymes involved in the metabolism of a large number of substrates [6], including numerous drugs, whose most constant characteristic is their low water solubility and high polarity, raising difficulties for their elimination through a water-rich medium, such as urine [7].

The diverse CYP450 isoenzymes catalyze different types of reactions in the form of oxidation, reduction or hydrolysis oxidation. These reactions require oxygen (O_2) and NADPH to oxidize the substrates through monooxidation reactions. The enzymes that catalyze this type of oxidation are called monooxygenases or mixed-function oxidases. The oxidations catalyzed by this enzyme system include: aromatic and aliphatic hydroxylations, N- and S-oxidations, epoxidations, O-, N-, and S-dealkylations, deaminations, desulfurizations, dehalogenations, and dehydrogenations.

The CYP450 system is configured into different isoenzymes that are named using a predefined system. The P450s are identified by the acronym CYP (for *cytochrome P*) followed by a number designating the family, a letter identifying the subfamily and another Arabic numeral corresponding to the gene (e.g. CYP1A1, CYP2C9).

These enzymes are found in the smooth endoplasmic reticulum of hepatocytes and jejunal intestinal epithelial cells, and are also found in the lung, brain and kidney. There are almost fifty isoenzymes in the human body, although the most numerous and, therefore, the most important, given that they are responsible for drug metabolism, are: CYP3A4, CYP2D6, CYP1A2, CYP2C9, CYP2C19, and CYP2E1 [8]. Of these, CYP3A4 is involved in the metabolism and interactions of almost 50% of drugs [9]. In addition, this isoenzyme is present in the intestinal mucosa and is therefore responsible for the first-pass metabolism of many drugs, which can, in some cases, significantly reduce their bioavailability [7,10].

One important characteristic of CYP450 isoenzymes is

Table 1 Effects of azoles on CYP450 isoenzymes and transport proteins. (Source: prescribing information. Spanish Agency of Medicines and Medical Devices)

Itraconazole	Potent CYP3A4 inhibitor, P-gp inhibitor and breast cancer resistance protein (BCRP) inhibitor.
Voriconazole	Inhibits CYP2C19, CYP2C9 and CYP3A4 enzymes.
Posaconazole	Potent CYP3A4 inhibitor.
Isavuconazole	Moderate CYP3A4/5 inhibitor, mild CYP2B6 inducer, mild P-gp inhibitor, mild inhibitor of organic cation transporter 2 (OCT2) and UGT.

P-gp: P-glycoprotein. UGT: UDP-glucuronosyltransferase.

their broad interindividual variability in relation to various factors, including the use of xenobiotics capable of increasing or reducing their enzymatic activity that can independently affect both liver and intestinal enzymes [11]. This suggests that there may be differences in the consequences of CYP3A4-inhibition interactions depending on the oral bioavailability of the substrates. For example, the impact of the consequences will be far greater on drugs with an elevated first-pass metabolism, since the effects of increased intestinal absorption will combine with those of reduced hepatic clearance. For substrates with high oral bioavailability, the interaction will only affect metabolism, resulting in a lesser impact on the bioavailability of the drug [10]. Similarly, a drug that is administered intravenously may have an inhibitory effect on hepatic CYP3A4, while when administered orally it will produce dual inhibition of both hepatic CYP3A4 and intestinal CYP3A4.

Inductors and inhibitors of isoenzymes produce their effects in a dose/concentration dependent manner but the timing is different because, while inhibition occurs immediately, induction requires protein synthesis and therefore can take up to 2 weeks to fully manifest [7–9].

The maximum impact of the inhibition of the activity of isoenzymes on pharmacokinetics lies in the drugs that are transformed and eliminated exclusively by the isoenzyme, since it cannot be eliminated until the inhibition disappears. In other cases, the effect may be much lower because there are other drug metabolism pathways that can somehow compensate for the deficient activity of the inhibited mechanism.

Transport proteins. The proteins that transport drugs through the body also play a relevant albeit lesser-known role in the origin of certain interactions [12]. Within this group of proteins, probably the best known and most studied is P-glycoprotein (P-gp). The physiological function of these proteins is to facilitate the active transport of various substrates and xenobiotics through the body, and they participate in facilitating or impeding intestinal absorption, biliary excretion, renal excretion, blood-brain barrier access, etc [13–16].

P-gp is a membrane glycoprotein predominantly found in cells of the liver, intestinal, renal, pancreas, and adrenal glands, among others. Its basic function is to excrete drugs into the bile, intestinal lumen, and urine, preventing access to the central nervous system at the blood-brain barrier [8]. Essentially, then, it prevents access by the drug to plasma while facilitating its elimination and preventing its access to brain tissue [17].

P-gp and CYP3A4 are expressed at the same time in the small intestine and liver and therefore, they may work in association to prevent drug absorption, the former by expelling them into the intestinal lumen and the latter by transforming them into metabolites [11]. The effect of P-gp may be saturated, in which case the molecules can reach venous territory as they are not expelled into the intestinal lumen. Highly lipid-soluble molecules can diffuse rapidly in this instance.

The synergistic effect on inhibition of P-gp and CYP3A4 leads to some important differences in practice. Fluconazole mildly/moderately increases immunosuppressant bioavailability, while ketoconazole produces a very intense effect, to the extent of being partially contraindicated. The explanation lies in the latter's ability to saturate P-gp compared to the absence of effects on P-gp of fluconazole. This difference is also present in relation to the route of administration: intravenous fluconazole mildly increases tacrolimus bioavailability while, with ketoconazole administered orally, the increase is very substantial [18–21].

The factors involved in the genesis and intensity of the consequences of this type of interaction are, nonetheless, highly diverse [22,23]. Some of the most relevant include sex, age, polymorphisms, and disease [10]. Logically, the variability in the pharmacokinetic processing of the substrate or drug altering the activity of isoenzymes and transport proteins is also clearly relevant [24].

QT interval prolongation. The QT interval is the electrocardiographic representation of the action potential duration of ventricular myocytes. Prolongation of this interval may be associated with torsades de pointes (TdP) ventricular tachycardia, syncope, and sudden cardiac death (SCD). The greater the prolongation of the QT interval, the more likely TdP and SCD are, especially if it is greater than 500 ms [25].

The mechanism most frequently linked to drug-induced QT prolongation is IKr channel blockade, likely facilitated by genetic predisposition. The enzyme system responsible for drug metabolism also plays a role, as this phenomenon is often concentration dependent. The presence of high concentrations facilitates channel blockade. Hence, inhibition of CYP450 activity, especially of isoenzymes CYP3A4 and CYP2D6, is usually a determining factor. As stated earlier, a number of factors commonly converge in its genesis, such as the combination of drugs that block ion channels, the combined use of any of these drugs with inhibitors of their metabolism, the presence of long QT syndrome (LQTS), bradycardia, female sex, advanced age, hypokalemia, hypomagnesemia, hypocalcemia, left ventricular dysfunction and heart failure, and previous history [25,26].

As we will explain, the problem may lie with some azole antifungals and amphotericin B itself, through hypokalemia in this case [27], a property shared by many of the drugs used in oncology-hematology. This circumstance explains why many of these drugs have contraindications or precautions in their prescribing information that include the consideration of carefully evaluating their association with other drugs that cause QT prolongation or any of the predisposing factors. We refer readers interested in reviewing this LQTS topic in greater detail to the more specific literature [28–31].

AZOLE ANTIFUNGALS

Itraconazole. A broad-spectrum antifungal drug [32] for oral or intravenous use, usually administered twice a day at daily doses ranging from 200 to 800 mg. It has an elimination half-life of 20–30 h in relation to auto-inhibition of its metabolism [33,34], which occurs via CYP3A4.

This azole acts as a potent inhibitor of the isoenzyme that metabolizes it, since the inhibitory constant (IC_{50}) for CYP3A4 is 0.0326 µM [35]. The most important metabolite is hydroxy-itraconazole, which is also metabolized through CYP3A4 [36]. Itraconazole exhibits some inhibitory activity against CYP2C9 and 2C19, although its inhibitory potency is lower: IC_{50} of 10 µM [35]. It likewise inhibits P-gp and BCRP [37].

Given this inhibitory potential, the drug's prescribing information [37] expressly recommends using it with caution with idelalisib, bosutinib, dasatinib, ibrutinib, nilotinib and vinca alkaloids. In general, they are not recommended and should be avoided even up to 2 weeks after itraconazole withdrawal. In the event that the combination is unavoidable, careful clinical monitoring is necessary and the dose should be reduced where not essential [37].

After completion of treatment, plasma concentrations of itraconazole decrease to a nearly undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. In patients with liver cirrhosis or in patients receiving CYP3A4 inhibitors, the decrease in plasma concentrations may be even more gradual. This is especially important when starting treatment with drugs whose metabolism is affected by itraconazole [37].

Itraconazole has been associated with QT interval prolongation and during interactions due to inhibition of the metabolism of other drugs, and with torsades de pointes [38-41]. Concomitant administration with CYP3A4 substrates that also prolong QT is contraindicated as it may result in elevated plasma concentrations, which may lead to increased or prolonged pharmacological effects, including adverse reactions, to such an extent that a potentially serious situation may arise.

Voriconazole. Voriconazole is one of the broad-spectrum azoles exhibiting *in vitro* activity against *Aspergillus*, *Candida*, *Scedosporium*, and some *Fusarium* species [42]. It has good oral bioavailability and sequential IV/PO therapy is possible. It is used in initial loading doses: 400 mg/12 h orally (PO) and 6 mg/kg every 12 h intravenously (IV). The maintenance dose is 200 mg/12 h and 4 mg/kg/12 h, PO/IV, respectively [43]. It produces auto-inhibition of its metabolism so the pharmacokinetics are not linear, since it undergoes a disproportionate increase in the area under the curve (AUC) and maximum plasma concentration (C_{max}) over time [44,45]. Voriconazole is metabolized through CYP2C19, with CYP3A4 and CYP2C9 also participating to a lesser extent [44]. *In vitro*, it behaves neither as a substrate nor as an inhibitor of P-gp [46,47]. Given its very broad pharmacokinetic variability, systematic monitoring of voriconazole plasma concentrations is recommended [48,49].

The available data indicate that the affinity of voriconazole for CYP3A4 is 50 times lower than for CYP2C9. [44] CYP2C19 activity is polymorphic [50–52].

Voriconazole is an inhibitor of the isoenzymes involved in its metabolism with IC_{50} values between approximately 8.5 (CYP2C) and 10.5 µM (CYP3A4) [53,35].

The prescribing information of this drug [43] points to the contraindication of voriconazole use with sirolimus or venetoclax given that voriconazole is likely to increase the plasma concentrations of both drugs and increase the risk of toxicity and, with the latter drug, tumor lysis syndrome [43].

Caution is advised when used in combination with glasdegib, since plasma concentrations of the latter drug may be elevated and there is a risk of QTc interval prolongation. If concomitant use cannot be avoided, frequent electrocardiogram monitoring is recommended.

Concomitant administration of voriconazole with tyrosine kinase inhibitors metabolized by CYP3A4 (such as bosutinib, dasatinib, nilotinib, ibrutinib, and ponatinib) is expected to increase plasma concentrations of the tyrosine kinase inhibitor and, with it, the risk of adverse reactions. If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring are recommended [43].

There is also a risk of interactions with some commonly used immunosuppressants, such as cyclosporine (a dose reduction to half the dose of cyclosporine is recommended) and tacrolimus (a reduction to one third of the original dose is recommended) [43].

Voriconazole has been associated with QT interval prolongation and torsades de pointes ventricular tachycardia. [54–58] Concomitant administration of voriconazole with other drugs that can prolong QT and whose metabolism can be reduced by the antifungal drug is contraindicated due to the risk of QT prolongation and associated torsades de pointes [43]. It should also be used with caution in combination with any other drug that may prolong QT.

Posaconazole. Triazole with broad antifungal spectrum used particularly in the treatment of infections caused by *Aspergillus, Fusarium*, and *Mucor*. It can be administered intravenously and orally, as a solution or tablets, the latter having better bioavailability. It has an elimination half-life of 30 hours, high plasma-protein-binding (>95%) and a high volume of distribution [59–61].

The usual dose in the treatment of invasive fungal infection is to administer a loading dose of 300 mg (three 100 mg tablets or 300 mg of concentrate for solution for infusion) twice a day on the first day and then 300 mg (three 100 mg tablets or 300 mg of concentrate for solution for infusion) once a day [62]. Given the wide variability of pharmacokinetic parameters, especially when the solution formulation is used, it is necessary to recommend the systematic monitoring of plasma levels [63, 64].

Posaconazole is a potent inhibitor of CYP3A4, with IC_{50} values of 1.3 µM. In tablet formulation, it has more intense interactions related to increased bioavailability [65]. It is also a substrate of P-gp and exhibits inhibitory capacity for the transport protein, with an IC_{50} of 3 µM [47]; interactions with digoxin through this mechanism have been described [66]. Its metabolism is through glucuronide conjugation, with little involvement of the oxidative system [62,67].

Its prescribing information establishes the contraindi-

cation to its combination with sirolimus and the risks related to toxicity due to vincristine or vinblastine, venetoclax, cyclosporine tacrolimus, and all-transretinoic acid, all due to an increase in their plasma levels versus a reduction in their clearance [62].

As with the other azoles, posaconazole has been implicated in cases of QT prolongation and polymorphic ventricular tachycardia [68-71]. In relation to this, concomitant administration is contraindicated with CYP3A4 substrates that can also cause QT prolongation which may be related to the plasma concentrations reached. In addition, it should be used with caution in combination with any other drug that may prolong QT [62].

Isavuconazole. The newest azole antifungal, authorized for use in the treatment of invasive aspergillosis and mucor infection [72]. It may be administered orally or intravenously, the latter in the form of isavuconazonium sulfate, which undergoes hydrolysis by plasma esterases to form isavuconazole extremely quickly. It has excellent PO bioavailability, a large volume of distribution and high plasma-protein-binding [73,74]. Unlike other antifungals in its group, there is less variability in its pharmacokinetic parameters, so the systematic monitoring of its plasma levels is not recommended [75–78]. It is administered with a loading dose of 200 mg every 8 h for the first 48 h, which is followed by a maintenance dose of 200 mg every 24 h. Isavuconazole is both a substrate and inhibitor of isoenzyme CYP3A4 [79,80].

In vivo studies indicate that this antifungal is a moderate inhibitor of CYP3A4 and may weakly induce CYP2B6, mildly affecting other isoenzymes [81]. Probably in relation to this characteristic, it has been repeatedly described that the intensity of the interaction of isavuconazole with CYP3A4 substrates, such as immunosuppressants, is clearly lower than that produced by the other azoles [82]. Co-administration of isavuconazole with tacrolimus, sirolimus, or cyclosporine produced an increase in the AUC of the immunosuppressants of 125%, 84%, and 29%, respectively, and, in the case of mycophenolic acid and prednisolone, of 35 and 8%, respectively. The C_{max} values of tacrolimus, sirolimus, and cyclosporine increased by 42%, 65%, and 6%, respectively, while the C_{max} of mycophenolic acid and prednisolone were 11% and 4% lower, respectively [82].

Isavuconazole is described in its prescribing information as a moderate inhibitor of CYP3A4/5. Therefore, systemic exposure to drugs metabolized by CYP3A4 may increase if administered together with isavuconazole. As noted, concomitant use of isavuconazole with CYP3A4 substrates such as the immunosuppressants tacrolimus, sirolimus, or cyclosporine may increase systemic exposure to these drugs. Finally, careful monitoring of any incidence of toxicity is recommended, along with a reduction, if necessary, in the dose of vincristine, vinblastine, imatinib or mitoxantrone [72].

The administration of isavuconazole together with various substrates of transporter proteins was associated with insignificant changes in the pharmacokinetic parameters of atorvastatin, digoxin, metformin, and methotrexate [83]. The IC_{50} of isavuconazole on P-gp was 3 μM [47].

The effect of isavuconazole versus moxifloxacin or placebo on cardiac repolarization has been evaluated in a randomized double-blind study in healthy volunteers treated with the antifungal drug, including loading doses at conventional regimen and with supratherapeutic doses, for 11 days. No effect on QT interval prolongation has been demonstrated. In this study, a QT shortening effect related to the plasma concentrations of the drug was evidenced [84–86]. Isavuconazole is therefore contraindicated in patients with familial short QT syndrome; caution is advised when administering isavuconazole to patients who are taking other drugs known to decrease the QT interval, such as the antiepileptic drug rufinamide [72].

DRUGS USED IN HEMATOLOGY-ONCOLOGY

Table 2 describes the drugs commonly used in the treatment of hematological tumors and rejection prophylaxis in hematopoietic cell transplantation. This information has been used to select the drugs described in greater detail below because they may be targets for interaction with azoles due to alterations in their metabolism or at the level of the QT interval.

Acalabrutinib. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue of the active site of Bruton's tyrosine kinase. As a result, it is indicated for the treatment of chronic lymphocytic leukemia. It is eliminated from the body through the participation of the CYP3A4 isoenzyme, and is a substrate of the P-gp and BCRP transporter proteins. It has an elimination half-life of 1–2 h [87].

It has been reported that administration with itraconazole can increase the bioavailability of acalabrutinib by 4.8- to 5.2-fold [88]. Hence, it is recommended that concomitant use with CYP3A/gp-P inhibitors be avoided. If CYP3A/gp-P inhibitors (e.g. itraconazole, posaconazole, or voriconazole) are to be used for a short period, treatment should be discontinued [87].

The effect of moderate CYP3A inhibitors has been evaluated in healthy subjects by administering 400 mg of fluconazole in a single dose or 200 mg of isavuconazole in repeated doses for 5 days. The mean C_{max} and AUC values of acalabrutinib increased 1.37 (1.14–1.64) and 1.60 (1.45–1.77) times with isavuconazole and 1.48 (1.10–1.98) and 2.16 (1.94–2.40) times with fluconazole. For the active metabolite ACP-5862, these values were 0.72 (0.63–0.82) and 0.91 (0.86–0.97) times with isavuconazole and 0.65 (0.49–0.87) and 0.5 (0.91–0.99) times when co-administered with fluconazole [89]. No dose adjustment of acalabrutinib is required in combination with moderate CYP3A inhibitors [87].

QT prolongation has not been described in patients treated with this drug [87].

Bortezomib. This proteasome inhibitor is **indicated** for the treatment of mantle cell lymphoma and multiple myeloma. Bortezomib is metabolized mainly by oxidation through CYP3A4, CYP2C19, and CYP1A2, although the main metabolic pathway is deboronation, through which two deboronated

Table 2 **Drugs used in the treatment of hematologic tumors. Enzymes involved in its metabolism, involvement of transport proteins, and potential for QT prolongation**

	Enzymes	Transport proteins	QT prolongation
Acalabrutinib	3A4	P-gp, BCRP	
Bendamustine	1A2		
Bleomycin	Hydrolases		
Bortezomib	1A2, 3A4, 2C9		YES
Bosutinib	3A4		YES
Carfilzomib	Peptidases		YES
Cyclophosphamide	?		YES
Cyclosporine	3A4	P-gp, OATP	
Cisplatin	-		
Cytarabine	Cytidine deaminase		
Cladribine	Not known		
Chlorambucil	Various		
Dacarbazine	1A2, 2E1		
Dasatinib	3A4		YES
Doxorubicin	2D6, 3A4	P-gp	
Duvelisib	3A4		
Etoposide	3A4, UGT	P-gp	
Fludarabine	Phosphorylation		
Gemcitabine	Cytidine deaminase		
Gilteritinib	3A4	P-gp, BCRP	YES
Glasdegib	3A4, 2C8, UGT1A9		YES
Hydroxyurea	Various		
Ibrutinib	3A4		
Idelalisib	1A2, 3A4, UGT, AO	P-gp	
Imatinib	3A4		YES
Lenalidomide	-	P-gp	YES
Melphalan	Degradation		
6-mercaptopurine	Xanthine oxidase, various		
Methotrexate	Various		
Mycophenolate	UGT1A9		
Midostaurin	3A4		
Mitoxantrone	Various	BCRP	
Nilotinib	3A4	P-gp	YES
Oxaliplatin	-		YES
Pentostatin	-		
Pomalidomide	1A2, 3A4		
Ponatinib	3A4		YES
Prednisone	3A4		
Ruxolitinib	2C9, 3A4		
Selinexor	3A4, UGT		
Sirolimus	3A4	P-gp	
tacrolimus	3A4		YES
Thalidomide	-		
All-transretinoic acid	3A4		YES
Arsenic trioxide	-		YES
Venetoclax	3A4		
Vinblastine	3A4		
Vincristine	3A4	P-gp	

AO: aldehyde oxidase. P-gp: P-glycoprotein, BCRP: breast cancer resistance protein. OATP: organic anion transporting polypeptide.

metabolites are formed that subsequently undergo hydroxylation. It has an elimination half-life of 40–193 h in relation to self-inhibition of its metabolism [90].

In a drug-drug interaction study conducted in 12 patients to evaluate the effect of ketoconazole on the pharmacokinetics of bortezomib, a mean bortezomib AUC increase of 35% was observed. (CI 90% [1.032 to 1.772]) [91]. Although the percentage is of little clinical significance, cases of paralytic ileus have been described in patients treated with bortezomib, voriconazole or itraconazole [92]. Close monitoring is recommended when bortezomib is administered in combination with potent CYP3A4 inhibitors [90].

Isolated cases of QT interval prolongation were described in clinical trials; although causality has not been established [93], caution is recommended.

Bosutinib. It is a BCR-ABL tyrosine kinase inhibitor, indicated for the treatment of chronic myelogenous leukemia [94]. It is metabolized by CYP3A4, so inhibition of the activity of this isoenzyme leads to reduced clearance and increased concentrations. It has an elimination half-life of 35.5 h [94].

In a study of 24 healthy subjects who were administered 5 doses of 400 mg/day of ketoconazole together with a single 100 mg fasting dose of bosutinib, the C_{max} of bosutinib was increased by 5.2-fold, and the plasma AUC of bosutinib by 8.6-fold [95].

In a study of 20 healthy subjects administered a single 125 mg dose of aprepitant, a moderate CYP3A inhibitor, together with a single 500 mg dose of bosutinib after food, aprepitant increased bosutinib C_{max} by 1.5-fold and bosutinib AUC in plasma by 2.0-fold [96].

It is recommended to avoid concomitant use of bosutinib with potent or moderate CYP3A inhibitors, selecting, whenever possible, an alternative drug whose CYP3A inhibitory potential is null or minimal. If a potent or moderate CYP3A inhibitor is required during bosutinib treatment, it should be considered whether to discontinue or reduce the dose of bosutinib treatment. Caution should be exercised if weak CYP3A inhibitors are used with bosutinib [94].

In a randomized, single-dose, double-blind, crossover, open-label, placebo- and moxifloxacin-controlled study, the effect of bosutinib 500 mg administration on corrected QTc was evaluated in healthy subjects. According to the data from this study, bosutinib does not appear to prolong QTc in healthy subjects at a dose of 500 mg per day with food, nor under conditions that result in the supratherapeutic elevation of plasma concentrations. Following single-dose oral administration of bosutinib 500 mg (therapeutic dose) and bosutinib 500 mg together with 400 mg of ketoconazole (to achieve supratherapeutic concentrations of bosutinib) in healthy subjects, the upper limit of the one-sided 95% confidence interval (CI) around the mean change in QTc interval was less than 10 ms at all post-dose administration time points, and no adverse events suggestive of QTc prolongation were observed [97]. In a study in subjects with impaired liver function, an increasing frequency of QTc interval prolongation >450 ms was observed as liver function declined [98].

In the phase 1/2 clinical study conducted in patients with previously treated Ph+ leukemia, changes in the QTcF interval that differed >60 ms from the baseline interval were observed in 6 (1.1%) out of 562 patients. In the phase 3 clinical study in newly diagnosed chronic phase CML patients treated with bosutinib 400 mg, no patients in the bosutinib treatment group had an increase >60 ms relative to baseline when the QT interval was corrected with Fridericia's formula (QTcF). In the phase 3 clinical study in patients with newly diagnosed Ph+ CML in chronic phase treated with bosutinib 500 mg, changes in the QTcF interval that differed >60 ms from baseline were observed in 2 out of 248 (0.8%) patients receiving bosutinib [94]. The proarrhythmic potential of bosutinib cannot be ruled out [99].

In the light of these data, bosutinib should be used with caution in patients who have or may have QT interval prolongation, including patients with any overlapping risk factors. It is advisable to monitor for any effect on QTc, and a baseline electrocardiogram (ECG) is recommended before starting bosutinib treatment and when clinically indicated. Hypokalemia or hypomagnesemia should be corrected prior to bosutinib administration, and plasma concentrations of these ions should be monitored periodically during treatment [94].

Carfilzomib. Carfilzomib is a proteasome inhibitor that is metabolized primarily by the peptidase and epoxide hydrolase pathway and, consequently, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers [100]. QT interval prolongation and ventricular tachycardia have been reported [101].

Cyclophosphamide. It is a phosphoramide-type antineoplastic, of the nitrogen mustard group. It is an electrophilic agent, which acts specifically during the S phase of the cell cycle. It reacts with nucleophilic atoms of the nucleic bases, forming inter- and intra-chain bridges in the double helix DNA, causing important interferences in the processes of DNA transcription and replication. It is indicated for the treatment of Hodgkin's lymphoma, non-Hodgkin's lymphomas, multiple myeloma, chronic lymphocytic leukemia (CLL) and acute lymphocytic leukemia (ALL), chronic myeloid leukemia, and acute lymphoblastic leukemia [102].

Increased exposure to cyclophosphamide metabolites has been reported in patients in treatment with itraconazole, fluconazole, and ketoconazole [102,103]. It has been suggested that, at least in the case of voriconazole, this effect could be caused by CYP2B6 inhibition [104]. In this regard, isavuconazole acts as an inducer of this isoenzyme, so it can *a priori* reduce cyclophosphamide concentrations with loss of efficacy [102], although some of the published data do not seem to confirm this [105].

Following exposure to treatment regimens that included cyclophosphamide, supraventricular arrhythmias (including

atrial fibrillation and flutter) and ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmias) have been reported in patients with and without other signs of cardiotoxicity [106].

Cyclosporine. Cyclosporine is a calcineurin inhibitor immunosuppressant indicated for the prevention of graft rejection after allogeneic bone marrow and stem-cell transplantation and in the prevention or treatment of graft-versus-host disease (GVHD). It is extensively metabolized, resulting in the formation of 15 metabolites. Metabolism takes place mainly in the liver, via CYP3A4 [107].

Caution should be exercised when cyclosporine is co-administered with drugs that produce CYP3A4 and/or P-glycoprotein inhibition. The azole antifungals: fluconazole, itraconazole and voriconazole can at least double exposure to cyclosporine [108–113].

In a retrospective study, information was collected from bone marrow transplant patients treated with tacrolimus or cyclosporine and fluconazole, isavuconazole, or posaconazole. The dose reduction percentage needed to maintain levels within the therapeutic range for the three azoles was 27, 12, and 13%, respectively [113].

In a study conducted in children with bone marrow transplant treated with cyclosporine or tacrolimus or sirolimus in which a dose of 100/200 mg of isavuconazole was used, no interactions were described [114].

A study was conducted to evaluate the effect of posaconazole 200 mg daily for 10 days on cyclosporine. Coadministration of posaconazole increased the bioavailability of cyclosporine and the dose should be reduced by 14–29% [115].

Dasatinib. Dasatinib is an inhibitor of several tyrosine kinases; BCR-ABL, SRC, c-KIT and PDGFR, which is indicated for the treatment of newly diagnosed chronic myelogenous leukemia (CML) in the chronic, accelerated or blastic phase, Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) and lymphoid blast crisis from CML. It is a substrate of the CYP3A4 isoenzyme, so potent inhibitors of this enzyme may increase its bioavailability. As a result, coadministration of potent CYP3A4 inhibitors in patients receiving dasatinib is not recommended. It has an elimination half-life of 3–5 h [116].

In a study in which dasatinib was administered with ketoconazole for 8 days, the C_{max} increased from 14 ng/mL on day 2 to 51 ng/mL on day 8. The AUC was 71 ng*h/mL and 345 ng*hour/mL, respectively. The C_{max} and AUC ratios, from day 8 to day 2, were 3.56 (90% CI, 2.86–4.44) and 4.84 (90% CI, 3.83–6.13), respectively. In addition, the elimination half-life increased from 3.3 hours to 8.7 hours [117]. Therefore, coadministration of potent CYP3A4 inhibitors is not recommended [116].

In vitro and in vivo data suggest that dasatinib has the ability to prolong ventricular cardiac repolarization (QT interval) [118,119]. In 258 patients treated with dasatinib and 258 patients treated with imatinib, after a minimum follow-up of 60 months in the phase 3 trial in patients with CML, QTc prolongation was reported as an adverse reaction in 1 patient (<1%) in each group. The median change in QTcF from baseline was 3.0 ms in dasatinib-treated patients compared with 8.2 ms in imatinib-treated patients. One patient (<1%) in each group experienced a QTcF >500 ms. In 865 patients with leukemia treated with dasatinib in phase 2 clinical studies, the mean change in QTc interval from baseline values using the Fridericia (QTcF) method was 4–6 ms, with an upper limit at the 95% confidence interval < 7 ms. Of the 2,182 patients with resistance or intolerance to prior imatinib therapy who received dasatinib in clinical trials, 15 (1%) patients had QTc prolongation as an adverse reaction and 21 patients (1%) had a QTcF >500 ms [116].

Dasatinib should be administered with caution in patients who have or may develop QTc prolongation. This includes patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic drugs or other drugs that cause QT prolongation, and patients in treatment with high cumulative doses of anthracyclines. Hypokalemia or hypomagnesemia should be corrected prior to dasatinib administration [116].

Doxorubicin. Doxorubicin is an anthracycline antibiotic, substrate of CYP3A4, CYP2D6 and P-glycoprotein. Clinically significant interactions with CYP3A4, CYP2D6 and/or P-glycoprotein inhibitors have been reported, resulting in increased concentrations and clinical effect of doxorubicin [120]. However, doxorubicin and ketoconazole have been evaluated in combination in the treatment of prostate cancer without reporting effects related to a possible interaction [121]. Doxorubicin has not been implicated in alterations of cardiac repolarization.

Duvelisib. Duvelisib is an inhibitor of phosphatidylinositol 3-kinase p110δ (PI3K-δ) and PI3K-γ indicated for the treatment of chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL). It is eliminated from the body after metabolism by CYP3A4 [122].

Concomitant administration of a strong CYP3A inhibitor, ketoconazole (200 mg twice daily for 5 days), with a single oral dose of 10 mg duvelisib in healthy adults (n = 16) increased 1.7-fold the C_{max} of duvelisib and 4-fold the AUC. It is recommended to reduce the dose to 15 mg twice daily when administered concomitantly with potent CYP3A4 inhibitors. No dose adjustment is necessary when administered with moderate CYP3A4 inhibitors, although potential adverse reactions to duvelisib should be closely monitored [122].

The effect of different doses of duvelisib 25 and 75 mg twice daily on the corrected QT interval (QTc) was evaluated in patients with previously treated hematologic malignancies. No increases >20 ms were observed in the QTc interval [122].

Etoposide. This is a cytostatic whose main effect appears to focus on double-strand DNA breaks through interaction

with topoisomerase II or through the formation of free radicals. It is indicated for the treatment of Hodgkin's lymphoma, non-Hodgkin's lymphoma, and acute myeloid leukemia [123].

It is a substrate of CYP3A4 and P-gp and undergoes glucuronide conjugation. Ketoconazole increases the AUC of etoposide by 20% so no dose adjustment is required; however, toxicity should be monitored [124].

Gilteritinib. Inhibitor of FMS-like tyrosine kinase-3 (FLT3) or fetal liver kinase 2, and AXL that is indicated for the treatment of acute myeloid leukemia with FLT3 mutation [125]. According to *in vitro* data, gilteritinib is metabolized primarily through CYP3A4. In addition, it is a substrate of P-gp and BCRP. Gilteritinib could inhibit BCRP, P-gp and OCT1 at clinically relevant concentrations [125].

In healthy subjects, a single 10 mg dose of gilteritinib administered with itraconazole (200 mg once daily for 28 days), resulted in an approximate 20% increase in mean C_{max} and a 2.2-fold increase in mean AUC compared to subjects given a single dose of gilteritinib [125]. Exposure to gilteritinib increased approximately 1.5-fold in patients with relapsed or refractory AML when it was co-administered with a potent inhibitor of CYP3A, P-gp and/or BCRP [126].

Potent inhibitors of CYP3A, P-gp and/or BCRP (voriconazole, itraconazole, posaconazole) may increase plasma concentrations of gilteritinib. Alternative drugs that do not strongly inhibit CYP3A, P-gp and/or BCRP activity should be considered. In situations where there are no suitable therapeutic alternatives, toxicity should be carefully monitored during the administration of gilteritinib [125].

Gilteritinib may prolong cardiac ventricular repolarization. QT interval prolongation can be observed in the first three months of treatment with this drug [127]. It is recommended to discontinue administration of the drug if the QTcF interval is greater than 500 ms and to resume treatment reducing the dose to 80 mg or 120 mg when the QTcF interval returns to within 30 ms of the baseline level or ≤480 ms. If an increase in the QTcF interval >30 ms occurs on ECG on day 8 of cycle 1, it should be confirmed by ECG on day 9, after which a dose reduction to 80 mg should be considered [125].

Glasdegib. It is an inhibitor of the Hedgehog signal transduction pathway that is indicated for the treatment of *de novo* or newly diagnosed secondary acute myeloid leukemia (AML) in adult patients who are not candidates for standard induction chemotherapy, in combination with low-dose cytarabine. CYP3A4 is responsible for most of the metabolism of glasdegib while CYP2C8 and UGT1A9 play a minor role [128].

Ketoconazole, at a dose of 400 mg once daily for 7 days, increased the mean area under the curve of glasdegib approximately 2.4-fold and the maximum plasma concentration by 40%, after administration of a single oral dose of 200 mg, in healthy subjects [129].

Caution should be exercised when it is administered concomitantly with the potent CYP3A4 inhibitors itraconazole, ketoconazole, posaconazole and voriconazole, since an increase in the plasma concentration of glasdegib may occur. If possible, an alternative concomitant drug with no or minimal CYP3A4 inhibitory potential is recommended [128].

In a randomized study in patients with high-risk acute myeloid leukemia and myelodysplastic syndrome treated with glasdegib and low-dose cytarabine versus low-dose cytarabine monotherapy, Grade 3/4 QT prolongations on ECGs were reported in 3.5% of patients treated with glasdegib and low-dose cytarabine compared to 2.4% of patients treated with low-dose cytarabine monotherapy [130].

Alternatives should be considered for drugs with known effects on QT prolongation and/or those that are potential potent CYP3A4 inhibitors [128].

Ibrutinib. This is a Bruton's tyrosine kinase (BTK) inhibitor used in the treatment of relapsed or refractory mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and Waldenström macroglobulinemia [131]. Ibrutinib is metabolized primarily by CYP3A4, generating a dihydrodiol metabolite with approximately 15-fold lower BTK inhibitory activity than ibrutinib. The involvement of CYP2D6 in the metabolism of ibrutinib appears to be minimal. It has an elimination half-life of 4–13 h [131].

Combination with CYP3A4 inhibitors alters the clearance of ibrutinib. Co-administration with itraconazole produces a 10-fold increase in the AUC of ibrutinib and an 8.8-fold increase in the C_{max} [132]. Concomitant administration of ketoconazole to 18 healthy, fasting volunteers increased the C_{max} and AUC of ibrutinib 29-fold and 24-fold, respectively. In patients with B-cell malignancies treated with ibrutinib, concomitant administration of voriconazole increased C_{max} 6.7-fold and AUC 5.7-fold [133,134].

Potent CYP3A4 inhibitors (itraconazole, voriconazole, and posaconazole) should be avoided. If the benefit outweighs the risk and a potent CYP3A4 inhibitor must be used, the dose of ibrutinib should be reduced to 140 mg during treatment with the inhibitor or ibrutinib should be temporarily discontinued, for 7 days or less. The patient should be closely monitored for toxicity, and dosage modification guidelines should be followed as needed [131].

Moderate CYP3A4 inhibitors produce a lower intensity effect, as has been shown with erythromycin, in patients with B-cell neoplasms in which the C_{max} and AUC of ibrutinib increased 3.4-fold and 3.0-fold, respectively. It is recommended to reduce the dose to 280 mg for as long as the inhibitor is used. The patient should be closely monitored for toxicity, and dosage modification guidelines should be followed as needed. Fluconazole – and probably isavuconazole – are part of this recommendation. As can be deduced from the results of a retrospective study in which information was collected from eight patients treated with the combination of isavuconazole (200 mg/day) and ibrutinib for fungal infection, the effect of this azole is minor. Five patients remained on the initial dose of ibrutinib (140–420 mg/day), while, in the remaining three,

the dose was reduced from 420/mg/day to 140–280 mg/day. In seven of the patients, the evolution of the fungal infection was adequate, with no adverse effects. In one patient, ibrutinib had to be discontinued due to thrombopenia after 128 days of combined treatment with isavuconazole [135].

No dose adjustment of ibrutinib appears necessary when combined with mild CYP 3A4 inhibitors, since it is estimated that the AUC may increase less than 2-fold. However, the patient should be closely monitored for toxicity, and dosage modification guidelines should be followed as needed [131].

The effect of ibrutinib on the QTc interval was evaluated in 20 healthy men and women in a randomized, double-blind, placebo-controlled, positive-controlled study. At the supratherapeutic dose of 1,680 mg, ibrutinib did not prolong the QTc interval in a clinically significant manner. The largest upper limit of the bilateral 90% CI for differences in the baseline-adjusted mean between ibrutinib and placebo was less than 10 ms. In the same study, a concentration-dependent reduction in the QTc interval (-5.3 ms [90% CI: -9.4, -1.1] was observed at a C_{max} of 719 ng/mL followed by a supratherapeutic dose of 1,680 mg [136].

Idelalisib. Idelalisib is an inhibitor of phosphatidylinositol 3-kinase p110δ (PI3K-p110) and Bruton's tyrosine kinase (BTK) protein, indicated for the treatment of chronic lymphocytic leukemia and follicular lymphoma. Idelalisib is metabolized mainly by an aldehyde oxidase and, to a lesser extent, by CYP3A and glucuronidation (UGT1A4). Its primary metabolite is GS-563117, which is not pharmacologically active. Idelalisib and GS-563117 are substrates of P-gp and BCRP. The elimination half-life is 8.2 hours (range: 1.9–37.2) [137].

In a clinical trial, concomitant administration of a single 400 mg dose of idelalisib with 400 mg once daily of ketoconazole was found to generate a 26% increase in the C_{max} and 79% increase in the AUC of idelalisib. [138] No initial dose adjustment of idelalisib is considered necessary when administered with CYP3A/P-gp inhibitors, but intensified monitoring for adverse reactions is recommended [137].

The effect of idelalisib (150 mg and 400 mg) on the QT/QTc interval was evaluated in a placebo- and positive-controlled crossover trial (moxifloxacin 400 mg) in 40 healthy subjects. At a dose 2.7 times the maximum recommended dose, idelalisib did not prolong the QT/QTc interval (<10 ms) [137].

Imatinib. Imatinib is a BCR-ABL tyrosine kinase inhibitor that can be used in the treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (BCR-ABL), Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), myelodysplastic/myeloproliferative syndromes, advanced hypereosinophilic syndrome and/or chronic eosinophilic leukemia. It has an elimination half-life of 18 h [139].

In vitro results show that CYP3A4 is the major human P450 enzyme catalyzing the biotransformation of imatinib. Inhibitors of CYP3A4 activity; azole antifungals including ketoconazole, itraconazole, posaconazole and voriconazole, could reduce metabolism and increase imatinib concentrations. There was a significant increase in exposure to imatinib. The mean C_{max} and AUC of imatinib increased by 26% and 40%, respectively, in healthy subjects when co-administered with a single dose of ketoconazole [139].

Experimental models have shown a clear effect of voriconazole on the clearance of imatinib, which is significantly reduced, with an increase in C_{max} of 36.8% [140]. Serious adverse effects in the form of a pustular rash, probably concentration dependent, have been described in a patient treated with voriconazole and imatinib [141]. Caution should be exercised when imatinib is administered with inhibitors of the CYP3A4 family.

Imatinib can cause QT prolongation in some patients, probably with a lower incidence than the other drugs used for the treatment of chronic myeloid leukemia [118,142].

Lenalidomide. Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1 (DDB1), cullin 4 (CUL4) and regulator of cullins 1 proteins (Roc1). In hematopoietic cells, lenalidomide bound to cereblon recruits the substrate proteins Aiolos and Ikaros, lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation, which produces direct cytotoxic and immunomodulatory effects. It is indicated for the treatment of multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma and follicular lymphoma [143].

In vitro, lenalidomide is a substrate of P-gp, but does not exhibit inhibitory capacity. P-gp inhibitors do not appear to have any relevant effects on lenalidomide pharmacokinetics [144].

Occasionally, arrhythmia, QT interval prolongation, atrial flutter and ventricular extrasystoles have been described among the infrequent adverse effects of the drug [143,145]. Lenalidomide did not produce QT alterations in a study performed with therapeutic and supratherapeutic doses [146].

Midostaurin. Midostaurin is an inhibitor of FLT3, KIT, PDGFR (platelet growth factor receptor) and VEGFR2 (vascular endothelial growth factor receptor 2), and serine/threonine kinase of the protein kinase C (PKC) family. It is indicated in the treatment of acute myeloid leukemia (AML) with FLT3 mutation in combination with standard induction (daunorubicin and cytarabine) and consolidation (high-dose cytarabine) chemotherapy, aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematologic neoplasm (SM-AHN), or mast cell leukemia (MCL). Its elimination half-life is 20.9 h [147].

Midostaurin undergoes extensive hepatic metabolism, mainly through CYP3A4, and transformed into the active metabolites CGP62221 and CGP52421. In a clinical trial of 36 healthy subjects, steady-state administration of ketoconazole with a single 50 mg dose of midostaurin resulted in a significant increase in midostaurin concentrations, C_{max} and AUC

were 1.8-fold and 10-fold higher, respectively. In addition, there was a 3.5-fold increase in the AUC of CGP62221 [148].

In a group of patients treated with itraconazole, a potent CYP3A4 inhibitor, at steady state, and with midostaurin at steady state (50 mg twice daily for 21 days), the steady state concentration of midostaurin, (C_{min}) increased 2.09-fold. The C_{min} of CGP52421 increased by a factor of 1.3, while no significant effect on CGP62221 exposure was observed [147].

Recently, an 8-fold increase in midostaurin concentration has been described when administered in association with posaconazole [149]. The use of isavuconazole and midostaurin is anecdotal, but the presence of interactions has not been described [150, 151].

Caution is recommended when potent CYP3A4 inhibitors are administered concomitantly with midostaurin because they may increase plasma concentrations of midostaurin. Alternative drugs that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity [147].

A specific study on the QT interval in 192 healthy subjects who received the 75 mg dose twice daily did not show that midostaurin or CGP62221 prolonged the QT interval in a clinically significant manner. However, this study was of insufficient duration to estimate the effects of the long-acting metabolite CGP52421 on QTc interval prolongation [152]. Consequently, a phase 2 clinical trial on 116 patients with ASM, SM-AHN, or MCL studied the change to QT corrected with Fridericia's formula (QTcF) with respect to baseline with the concentration of midostaurin and each metabolite, and the result showed that neither midostaurin, nor CGP62221 or CGP52421 appeared to be able to cause a clinically significant prolongation of QTcF. In the ASM, SM-AHN and MCL population, 25.4% of patients had at least one QTcF measurement greater than 450 ms and 4.7% greater than 480 ms on ECG [147].

Therefore, caution should be exercised in patients at risk of QTc prolongation (e.g. due to concomitant medications and/or electrolyte disturbances). If midostaurin is taken with other drugs that prolong the QT interval, consideration should be given to assessing the QT interval by ECG. If QT prolongation is detected, the dose should be adjusted [147].

- QTc interval >470 ms and ≤500 ms

Decrease the dose to 50 mg once daily for the remaining cycle. Restart at the initial dose in the next cycle if the QTc interval improves to ≤470 ms at the start of the cycle. Otherwise, continue with midostaurin 50 mg once daily.

- QTc interval >500 ms

Stop or discontinue in the remaining cycle. If, just before the next cycle, the QTc interval improves to ≤470 ms, restart at the initial dose. If the QTc interval does not improve at the beginning of the next cycle, do not administer during that cycle. Midostaurin can be stopped for as many cycles as necessary until the QTc interval improves.

Nilotinib. Nilotinib is a potent inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein. It also inhibits PDGF, KIT and Ephin receptor kinases. It is indicated for the treatment of Philadelphia chromosome positive chronic myeloid leukemia. Nilotinib is metabolized primarily in the liver by CYP3A4, the expected major oxidative metabolizer, and nilotinib is also a substrate of P-gp [153]. Its elimination half-life is 17 h.

Exposure to nilotinib in healthy subjects increased 3-fold when co-administered with ketoconazole [154]. Therefore, concomitant treatment with potent CYP3A4 inhibitors, including ketoconazole, itraconazole, voriconazole, should be avoided. Increased exposure to nilotinib may also be expected with moderate CYP3A4 inhibitors. Alternative concomitant medications with no or minimal inhibition of CYP3A4 should be considered [153].

In the phase III trial in newly diagnosed chronic phase CML patients receiving 300 mg of nilotinib twice daily, the change in mean QTcF interval time from baseline at steady state was 6 ms. No patient presented a QTcF >480 ms. No episodes of torsades de pointes were observed. In a trial with healthy volunteers with exposures comparable to those observed in patients, no clinically relevant arrhythmias were observed [153]. However, nilotinib has been shown to prolong ventricular cardiac repolarization in a concentration-dependent manner in both adult patients and children [155,156].

Nilotinib may produce significant QT interval prolongation when administered with potent CYP3A4 inhibitors, with drugs with a known ability to prolong the QT interval and/or with food. The presence of hypokalemia and hypomagnesemia may increase this effect. Nilotinib should be used with caution in patients who have or are at significant risk of developing QTc interval prolongation [153].

Oxaliplatin. Oxaliplatin interacts with DNA forming inter- and intra-strand cross-links causing disruption of DNA synthesis resulting in cytotoxic and anti-tumor effects [157].

QT prolongation and torsades de pointes have been described in patients treated with oxaliplatin [158,159]. The QT interval should be closely and regularly monitored before and after oxaliplatin administration. Caution should be exercised in patients with a history of or a predisposition for QT prolongation, those taking medications known to prolong the QT interval, and those with electrolyte imbalances such as hypokalemia, hypocalcemia, or hypomagnesemia. In case of QT prolongation, treatment with oxaliplatin should be discontinued [157].

Pomalidomide. Indicated for the treatment of multiple myeloma, it is partly metabolized by CYP1A2 and CYP3A4/5. It is also a substrate for P-gp [160]. Concomitant administration of pomalidomide with ketoconazole, a potent inhibitor of CYP3A4/5 and P-gp, demonstrated no clinically relevant effect on pomalidomide exposure [160,161]. In a study in healthy volunteers that compared the effect on QT of pomalidomide 4 mg, 20 mg, and moxifloxacin 400 mg, pomalidomide did not

generate ECG alterations, versus the evident QT prolongation produced by fluoroquinolone [162].

Ponatinib. Ponatinib inhibits the activity of BCR-ABL and RET, FLT3 and KIT and members of the FGFR, PDGFR and VEGFR kinase families. It is indicated for the treatment of chronic phase chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). It has an elimination half-life of 22 hours [163]. Ponatinib is metabolized by the action of CYP3A4. Concomitant administration of a single 15 mg oral dose of ponatinib and ketoconazole 400 mg daily moderately increased systemic exposure to ponatinib; the AUC and C_{max} values of ponatinib were 78% and 47% higher, respectively, than those observed when ponatinib was administered as monotherapy [164]. Caution is required and a reduction of the initial dose of ponatinib to 30 mg should be considered when it is used concomitantly with strong CYP3A inhibitors.

The potential of ponatinib to prolong the QT interval was evaluated in 39 leukemia patients; no clinically significant prolongation of the QT interval was observed [165]. However, a thorough study of the QT interval has not been performed, so a clinically important effect on QT cannot be ruled out, and it is considered a risk drug.

Prednisone. Most corticosteroids undergo metabolism through CYP3A4. Concomitant treatment with CYP3A inhibitors such as ketoconazole and itraconazole has been shown to reduce corticosteroid clearance, increasing the risk of systemic adverse reactions [167]. This combination should be avoided unless the benefit outweighs the risk, in which case patients should be monitored for systemic reactions to corticosteroids [167].

No association has been described between the use of corticosteroids and the presence of QT prolongation or with torsades de pointes.

Ruxolitinib. Ruxolitinib is a selective inhibitor of the Janus-associated kinases (JAKs): JAK1 and JAK2. It is indicated for the treatment of myelofibrosis and polycythemia vera. It has an elimination half-life of 3 hours. Ruxolitinib is eliminated through metabolism by CYP3A4 and CYP2C9. Therefore, drugs that inhibit these enzymes may cause increased exposure to ruxolitinib [168].

In healthy subjects the co-administration of ruxolitinib, 10 mg single dose, with a potent CYP3A4 inhibitor, ketoconazole, increased the C_{max} and AUC of ruxolitinib by 33% and 91%, respectively. With concomitant administration of ketoconazole, the half-life was prolonged from 3.7 to 6.0 hours [169].

When administering ruxolitinib together with potent CYP3A4 inhibitors, including itraconazole, voriconazole and posaconazole, the dose of ruxolitinib should be reduced by approximately 50%, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dosage should be titrated based on safety and efficacy [168]. If ruxolitinib is administered together with potent CYP3A4 inhibitors or dual inhibitors of the CYP3A4 and CYP2C9 enzymes (e.g. fluconazole), the dose of Jakavi should be reduced by approximately 50%, and administered twice daily [168].

In healthy subjects, co-administration of ruxolitinib, 10 mg single dose, with erythromycin, a moderate CYP3A4 inhibitor, 500 mg twice daily for four days resulted in ruxolitinib C_{max} and AUC values that were higher by 8% and 27%, respectively [169]. No dose adjustment is required when ruxolitinib is administered with mild or moderate CYP3A4 inhibitors. However, patients should be closely monitored.

In healthy subjects, concomitant administration of ruxolitinib, 10 mg as a single dose, and a dual CYP2C9 and CYP3A4 inhibitor, fluconazole, elevated the C_{max} and AUC of ruxolitinib by 47% and 234%, respectively [170]. When using drugs that are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole), a 50% dose reduction should be considered. The concomitant use of ruxolitinib with daily doses of fluconazole greater than 200 mg should be avoided. It has been reported that the co-administration of 400 mg daily of voriconazole with ruxolitinib was effective and well tolerated, despite being a dual inhibitor of CYP3A4 and CYP2C9 [171].

In a detailed study of the QT interval in healthy subjects, no indication of a QT/QTc prolonging effect was observed when ruxolitinib was administered at single doses up to a supratherapeutic dose of 200 mg, indicating that ruxolitinib has no effect on cardiac repolarization [172].

Selinexor. Selinexor is a covalent and reversible selective inhibitor of nuclear export (SINE) that specifically blocks exportin 1 (XPO1). XPO1 is the primary mediator of nuclear export of a large number of cargo proteins, including tumor suppressor proteins (TSPs), growth regulators and growth-promoting (oncogenic) protein mRNAs. It is indicated for the treatment of multiple myeloma. Selinexor is metabolized by CYP3A4, various UDP-glucuronosyltransferases (UGTs) and glutathione-S-transferases (GSTs) [173].

No specific clinical studies on drug-drug interactions have been performed. A 30–40% increase in the AUC of selinexor when the drug was administered with azole antifungals has been described in a study in rats [174]. Dosage adjustments may not be necessary when the drug is used in combination with potent CYP3A4 inhibitors, although caution should be exercised.

The effect of various doses of selinexor up to 175 mg twice weekly on the QTc interval was evaluated in patients with hematologic malignancies in whom several treatments had been administered previously. Selinexor did not have a large effect (i.e. no greater than 20 ms) on the QTc interval when administered at the therapeutic dose level [173].

Sirolimus. Sirolimus binds to the specific cytosolic protein FKPB-12 forming an FKPB 12-sirolimus complex that inhibits the activation of the mammalian target of rapamycin molecule (mTOR), a critical kinase for cell cycle progression [175].

Sirolimus is extensively metabolized in the intestinal wall and liver by the CYP3A4 isoenzyme. Sirolimus is also a substrate for P-gp located in the small intestine. Administration of repeated doses of ketoconazole significantly altered sirolimus exposure when administered as an oral solution, with increases in sirolimus C_{max}, t_{max} and AUC values by 4.4-fold, 1.4-fold and 10.9-fold, respectively. [176] Co-administration of sirolimus and ketoconazole is not recommended [175].

Co-administration of sirolimus, a single dose of 2 mg, with multiple doses of oral voriconazole, 400 mg every 12 hours on day 1, then 100 mg every 12 hours for 8 days, in healthy subjects has been reported to increase the C_{max} and AUC of sirolimus by 7- and 11-fold, respectively. Co-administration of sirolimus and voriconazole is not recommended, although it has been suggested that, if used together, the dose of the immunosuppressant should be reduced by 50% [177] and 90% [178].

With posaconazole, the dose should be reduced by 60–80% [179,180], although some agencies have considered it necessary to contraindicate the combined use of sirolimus and posaconazole, describing that the administration of 200 mg of the antifungal drug in tablet form can increase the C_{max} and AUC of the immunosuppressant by 527% and 788%, respectively [62].

Isavuconazole also increases the AUC of sirolimus, but by much less: about 1.5 times, so the need for initial dose adjustment is less important [181].

Tacrolimus. Tacrolimus binds to a cytosolic protein forming a complex, FKBP12-Tacrolimus, which specifically and competitively binds to and inhibits calcineurin. This results in a calcium-dependent inhibition of T-cell signal transduction pathways, which prevents transcription of a discrete set of lymphokine genes. Tacrolimus is metabolized by CYP3A4 and undergoes the intestinal first-pass effect through the intervention of this isoenzyme [182].

Voriconazole significantly increases the tacrolimus concentration/dose ratio from 172.8 to 537.5 [183]. The increased bioavailability of tacrolimus is higher when voriconazole is switched from the intravenous to the oral route, as a result of the alteration of intestinal CYP3A4 that occurs with the oral route and is absent with intravenous administration [184]. It has been suggested that the dose of tacrolimus be reduced by at least 50% when initiating treatment with voriconazole [185].

With posaconazole, the AUC of tacrolimus increases 3-fold in lung transplant patients treated with antifungal tablets [186]; a 50% [187] or 60–70% reduction in the dose of the immunosuppressant is recommended [188]. The administration of posaconazole at a dose of 400 mg together with tacrolimus increased the C_{max} and AUC of tacrolimus by 121% and 358%, respectively [115].

With isavuconazole, it does not appear necessary to adjust the tacrolimus dose at the start of treatment [189], although it has been recommended that an initial tacrolimus dose of 0.017 mg/kg be administered instead of the usual 0.02 mg/kg [190]. In the case of liver transplantation, a 30% dose reduction was recommended [191]. The combination of isavuconazole and tacrolimus increased the concentration/dose ratio of the immunosuppressant 1.42-fold in the first week of treatment [181].

In a retrospective study with information collected from bone marrow transplant patients treated with tacrolimus and fluconazole, isavuconazole, or posaconazole, the percentage dose reduction needed to maintain levels within the therapeutic range for the three azoles was 25, 21 and 53%, respectively [192].

Occasional cases of QT prolongation associated with tacrolimus have been reported [193], so close monitoring of blood levels and assessment of the QT interval, renal function, and other adverse effects of tacrolimus is recommended when drugs with the potential to alter CYP3A4 metabolism are used concomitantly, and the tacrolimus dose should be discontinued or adjusted appropriately to maintain similar tacrolimus exposure [193,194].

All-transretinoic acid. It is indicated for the treatment of acute promyelocytic leukemia [195]. Tretinoin is metabolized by CYP26A1 in addition to CYP3A4. Compounds that inhibit CYP26A1, such as ketoconazole, could result in increased exposure to tretinoin. There is still no clinical evidence on the relative involvement of this enzyme in the general metabolism of tretinoin [195].

Increased tretinoin toxicity has been reported (e.g. pseudotumor cerebri, hypercalcemia) when azole antifungals were administered (e.g. fluconazole, voriconazole, posaconazole). This appears to be the result of a pharmacokinetic interaction involving mainly CYP3A4 [196,197]. The possibility of reducing the tretinoin dose should be considered [195].

QTc prolongations were observed with tretinoin and arsenic trioxide combination therapy. This could lead to torsades de pointes arrhythmias. For the treatment of QTc prolongation, ECG monitoring prior to and during treatment is recommended, especially for patients with risk factors [198].

Arsenic trioxide. The metabolism of arsenic trioxide involves the oxidation of arsenious acid, the active species of arsenic trioxide, to arsenic acid, as well as oxidative methylation to monomethylarsonic and dimethylarsinic acid mediated by methyltransferases, which takes place mainly in the liver. It is indicated for the treatment of acute promyelocytic leukemia [199].

Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. Prolongation of the QT interval can produce ventricular arrhythmia in torsades de pointes, which can lead to death. Prior treatment with anthracyclines may increase the risk of QT interval prolongation. The risk of ventricular tachycardia in torsades de pointes is higher in patients who are receiving or have received drugs that cause hypokalemia or hypomagnesemia, such as diuretics or am-

Table 3 Azoles in hematology-oncology. Recommendations

	Itraconazole	Posaconazole	Voriconazole	Isavuconazole
Acalabrutinib	Avoid or reduce the dose of acalabrutinib to 100 mg/day			No dose titration. Monitor adverse effects
Bortezomib	Caution (1)			Probably without risk
Bosutinib	Avoid. Risk of QT prolongation due to elevated bosutinib concentrations			Caution. (2) Reduce the dose by 50%
Carfilzomib	Caution. Risk of QT prolongation			Without risk
Cyclophosphamide	Caution: May increase cyclophosphamide levels with potential risk of QT prolongation			Risk of potential ineffectiveness (3)
Cyclosporine	Caution. Elevated cyclosporine levels	Reduce cyclosporine dose by 75%	Reduce cyclosporine dose by 50 %	Caution (4)
Dasatinib	Avoid. Risk of QT prolongation due to elevated dasatinib concentrations			No dose titration. Monitor adverse effects
Doxorubicin	No dose titration. Monitor adverse effects			
Duvelisib	Reduce duvelisib dose to 15 mg twice daily			No dose titration. Monitor adverse effects
Etoposide	No dose titration. Monitor adverse effects			
Gilteritinib	Avoid or closely monitor			No dose titration. Monitor adverse effects
Glasdegib	Avoid. Risk of QT prolongation due to elevated glasdegib concentrations			Without risk
Ibrutinib	Avoid	Caution (5)		Caution (6)
Idelalisib	Without risk			
Imatinib	Caution (7)			
Lenalidomide	No dose titration. Monitor adverse effects (8)			No dose titration
Midostaurin	Caution. Alternative drugs that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity.			Monitor adverse effects
Nilotinib	The administration of nilotinib with drugs that are strong CYP3A4 inhibitors should be avoided (9)			No dose titration. Monitor adverse effects
Oxaliplatin	No dose titration. Monitor adverse effects (8)			No dose titration
Pomalidomide	No dose titration. Monitor adverse effects			
Ponatinib	Caution, consider reducing the starting dose of ponatinib to 30 mg			No dose titration. Monitor adverse effects
Prednisone	Caution (10)			Caution (11)
Ruxolitinib	Caution	Reduce ruxolitinib dose by 50%		No dose titration. Monitor adverse effects
Selinexor	No dose titration. Monitor adverse effects			
Sirolimus	Avoid			Caution (4)
tacrolimus	Caution (12)	Reduce tacrolimus dose by one third		Caution (4)
All-transretinoic acid	Caution (13)			No dose titration. Monitor adverse effects
Arsenic trioxide	Caution (8)			Without risk
Venetoclax	Avoid (14)			Reduce the daily dose by 50%
Vinblastine	Avoid	Caution (15)	Caution (16)	Caution (16)
Vincristine	Avoid	Caution (15)	Caution (16)	Caution (16)

(1): Paralytic ileus cases have been described in patients treated with bortezomib, voriconazole or itraconazole.
(2) It can likely be used with caution since the contraindication is due to the risk of QT prolongation relating to increased concentrations due to CYP3A5 inhibition, which are lower with this drug.
(3): Isavuconazole is a mild inducer of CYP2B6.
(4) If necessary, monitor plasma levels to adjust the dose of the immunosuppressant.
(5): Reduce the dose to 140 mg/day in B-cell tumors and to 280 mg/day in the case of graft-versus-host disease.
(6) Reduce the dose to 280 mg/day in B-cell tumors and to 420 mg/day in graft-versus-host disease.
(7) Careful monitoring of any incidence relating to drug toxicity. Reduce the dose if necessary.
(8) Potential risk; both drugs can prolong QT.
(9) Significant QT interval prolongation can occur when nilotinib is administered inappropriately with potent CYP3A4 inhibitors.
(10) Risk of increased corticosteroid concentrations. Monitor adverse effects.
(11) Co-administration should be avoided unless the potential benefit outweighs the risk of increased concentrations.
(12) Use only if there are no other alternatives.
(13): Increased tretinoin concentrations with risk of toxicity. Monitor plasma calcium levels and assess dose reduction.
(14) Avoid at initiation and during the dose-titration phase; risk of tumor lysis syndrome. Reduce the daily dose of venetoclax by 75% when administered as a fixed daily dose.
(15) Only use when there are no alternative antifungal treatment options.
(16) Risk of neurotoxicity due to high concentrations of alkaloids. It may be necessary to reduce the dose.

photericin B. Caution is advised when arsenic trioxide is administered concomitantly with other drugs that prolong the QT/QTc interval, or drugs that cause hypokalemia or hypomagnesemia [200–202].

Venetoclax. Venetoclax is a potent and selective inhibitor of the anti-apoptotic protein BCL-2 (B-cell lymphoma). It is used in the treatment of chronic lymphocytic leukemia and acute myeloid leukemia. It has an elimination half-life of 26 hours. Venetoclax is metabolized mainly by CYP3A [203].

In a study in 11 patients, concomitant administration of ketoconazole 400 mg once daily for 7 days increased venetoclax C_{max} 2.3-fold and AUC 6.4-fold [204]. Compared with monotherapy administration of 400 mg venetoclax, concomitant administration of posaconazole 300 mg, venetoclax 50 mg and 100 mg for 7 days in 12 patients increased the C_{max} and AUC of venetoclax 1.6- and 1.9-fold, and 1.9-, and 2.4-fold, respectively [205].

Concomitant administration of venetoclax with other potent CYP3A4 inhibitors is expected to increase the AUC by an average of 5.8- to 7.8-fold [203].

In an uncontrolled study, the administration of conventional doses of isavuconazole as antifungal prophylaxis in 65 patients with acute myeloid leukemia or myelodysplastic syndrome, 49% of whom were treated with venetoclax, was effective and well tolerated, with no significant adverse effects reported [206].

Concomitant use of venetoclax with moderate or strong CYP3A inhibitors increases the C_{max} and AUC of venetoclax and may increase the risk of tumor lysis syndrome (TLS) and other toxic effects, at initiation and during the dose-titration phase. In patients with CLL, concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated. If the use of a CYP3A inhibitor is essential, the below recommendations should be followed:

Strong inhibitor

Initiation and dose-titration phase

- LLC: contraindicated
- AML: Day 1: 10 mg, Day 2: 20 mg. Day 3: 50 mg. Day 4: 100 mg or less

Fixed daily dose (after the dose titration phase: reduce the dose of venetoclax to 100 mg or less (or by at least 75% if already modified for other reasons).

Moderate CYP3A4 inhibitor

Reduce the dose of venetoclax by at least 50%. In CLL patients, avoid concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase. Consider alternative medications or dose reduction as described [203].

Co-administration of venetoclax and posaconazole is contraindicated [62].

Patients should be monitored more closely for signs of toxic effects and further dose adjustment may be required. The dose of venetoclax used prior to initiating administration of a CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor.

Venetoclax produced no effects on the QTc interval and there was no relationship between drug exposure and change in interval, even when administered at doses of 1200 mg [207].

Vinblastine. Vinblastine binds to tubulin and alters microtubule function, preventing polymerization and inducing depolymerization of the microtubules. It is metabolized by CYP3A4 and is a substrate of P-gp [208,209].

Vinblastine should be administered with caution in patients who are concomitantly taking drugs known to inhibit the metabolism of the drug through hepatic cytochrome CYP3A isoenzymes, or to patients with hepatic dysfunction. Concomitant administration of vinblastine and an inhibitor of this metabolic pathway may cause a more rapid onset and/or increased severity of side effects [209,210]. Concurrent use with itraconazole is contraindicated.

Vincristine. Vincristine sulfate affects cell mitosis by binding or crystallizing critical microtubular proteins of the mitotic spindle, such as tubulin, leading to arrest of cell division during metaphase and cell death. It is eliminated through CYP3A4 metabolism and is a P-gp substrate. It is indicated in the treatment of acute leukemia and malignant lymphomas, including Hodgkin's disease, non-Hodgkin's lymphomas (lymphocytic, mixed cell, histiocytic, undifferentiated, nodular and diffuse) [211].

Concomitant administration of vincristine sulfate with itraconazole or fluconazole (CYP3A4 inhibitors) has been associated with early onset and/or increased severity of neuromuscular adverse effects. Although there are no *in vivo* or *in vitro* studies, itraconazole, voriconazole, and posaconazole may increase plasma concentrations of vinca alkaloids, including vincristine sulfate, and may cause toxicity. Special caution should be exercised in patients under treatment with drugs that inhibit/induce hepatic metabolism by acting on cytochrome P450 isoenzymes, specifically in the CYP3A subfamily, or in patients with hepatic impairment [212–215]. It is recommended that dose titration of vincristine sulfate be considered. At present, no cases of toxicity related to the combination of vincristine with isavuconazole have been published.

CONCLUSIONS AND RECOMMENDATIONS

A review of the recommendations in Table 3 leads us to confirm the differences in potential for interactions among the various antifungals in relation to their inhibitory potency, especially of CYP3A4, and their ability to alter cardiac repolarization with the corresponding risk of prolonging electrocardiographic QT. Three drugs – itraconazole, voriconazole, and posaconazole – are relatively similar in promoting interactions with hematology-oncology drugs, relating to their ability to potently inhibit CYP3A4 and the added risk of prolonging QT. The remaining drug in this family, isavuconazole, has less in-

hibitory potency and no risk of QT prolongation. The latter is also a safer drug with fewer contraindications; it requires less vigilance and does not require monitoring of plasma levels for dose adjustment, as is recommended for the others. In addition, it can be used safely in patients with predisposing factors for QT prolongation [216–217].

CONFLICT OF INTEREST

JRA has received honoraria for talks on behalf of Pfizer, GSK, Menarini, Shionogi and MSD.

JB has received honoraria for talks on behalf of Pfizer, Gilead, Shionogi, and MSD.

LV has received honoraria for talks on behalf of Astellas, Gilead, MSD, Pfizer, Janssen, Astra Zeneca and GSK, and has received honoraria for consulting from Astellas, Gilead, Pfizer, and GSK

MK has received honoraria for lectures and consulting from Gilead, Jazz, Pfizer

LY has received honoraria for talks on behalf of Janssen, Abbvie, Gilead-Kite, Roche, Novartis, MSD, Pfizer, AstraZeneca, Novartis, Beigene, Lilly, has received honoraria for advisory board from Janssen, Abbvie, Gilead-Kite, Roche, Jazz, Sandoz, Celgene, MSD, Pfizer, AstraZeneca, BeiGene, Lilly, Alexion, and research funds from Janssen

JMA has been a consultant to and on the speakers bureau for Pfizer, Gilead, Merck Sharp and Dohme, and United Medical-Biotoscana.

IRC has received honoraria for talks on behalf of MSD, gilead, Astra Zeneca, Pfizer, GSK, Jansenn, and BMS and has received honoraria for advisory board from Pfizer, GSK, Astra Zeneca, and Gilead

JF has participated in scientific events or received remuneration in the form of research support or oral presentations from Merck, Pfizer, Gilead, MSD, Astellas, Novartis, and Roche.

MS has participated in advisory board or received honoraria for talks on behalf of Gilead, Menarini, MSD, Pfizer and Shionogi

CG received research support from Merck and Pfizer and honoraria for talks sponsored by Merck, Gilead, and Pfizer, and Shionogi.

CG-V has received honoraria for talks on behalf of Gilead Science, MSD, Novartis, Pfizer, Janssen, Menarini, GSK and Sanofi, as well as a grant from Gilead Science, Pfizer, and GSK.

PG-S has participated in advisory board or received honoraria for talks on behalf of Pfizer, MSD, Gilead, Astellas, and Abbvie.

CDG has participated in advisory board or received honoraria for talks on behalf of MSD, Pfizer, Shionogi, Menarini, Gilead, Janssen, ViiV, Roche and GSK

Rest of authors have no conflict of interest.

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