ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 11, Issue, 10, pp. 51046-51051, October, 2021
https://doi.org/10.37118/ijdr.23082.10.2021

RESEARCH ARTICLE OPEN ACCESS

WHAT IS THE BEST ANTIDEPRESSANT CHOICE IN HEPATIC DYSFUNCTION ACCORDING TO PHARMACOKINETICS CHARACTERISTICS?

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ARTICLE INFO

Article History:
Received 24th August, 2021
Received in revised form
06th September, 2021
Accepted 02nd October, 2021
Published online 30th October, 2021

Key Words:
Antidepressants can cause a temporary increase in transaminase levels due to extensive metabolism being more pronouncedin patients with liver dysfunctionmaking it difficult to treat depression. Among the antidepressants, desvenlafaxine present the best pharmacokinetics characteristics and is the most suitable for the treatment of depression in patients with liver dysfunction.

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ABSTRACT

Many patients with liver failure use antidepressants extensively metabolized by the liver, making them more sensitive to adverse effects. We aimed to assess the pharmacokinetic characteristics of antidepressants to determine the most suitable drugs in liver failure. Books and databases were used for research. The descriptors used were antidepressants, liver failure, and pharmacokinetics. 18 antidepressants were revised. Among the classes of antidepressants are monoamine oxidase inhibitors (IMAOS), tricyclic antidepressants (ADTs), selective serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SNRI), antagonists of serotonin receptors (AR 5HT), and atypical antidepressants (ADA). All antidepressants show some degree of metabolization, with a small percentage of drugs excreted unchanged in the urine. The best antidepressant options for patients with liver failure is desvenlafaxine. This drug is an active metabolite of venlafaxine, with high percentage of unchanged metabolites eliminated in the urine. Desvenlafaxine present dose adjustments already established in these cases, and not showed liver abnormalities without increase in the level of transaminases. Along with efficacy, pharmacokinetic characteristics should be considered, especially metabolism, when prescribing antidepressants to patients with liver failure. Furthermore, close accompaniment is essential to avoid overload and liver damage.

Citation: ***Tatiane Tonielo, Karini da Rosa, Cassiano Mateus Forcelini, Luciana Grazziotin Rossato-Grando et al.*** "What is the best antidepressant choice in hepatic dysfunction according to pharmacokinetics characteristics?*", International Journal of Development Research*, 11, (10), 51046-51051.

INTRODUCTION

The liver is a complex organ involved in several physiological functions. The hepatocytes are able of regeneration, protecting against injury caused by viruses, medication, alcohol, trauma, or partial hepatectomy. However, the regeneration of hepatocytes is limited and when exceeded, progressive damage can lead to liver failure. Besides to liver failure presented by the patient, some drugs may also be responsible for promoting liver injury. Drug-induced liver injury (DILI) is a serious adverse event that can occur during pharmacotherapy (Watkins and Seeff 2006; Lee 2013). Drugs appear to be responsible for 10–52% of all causes of acute liver failure (Larrey and Pageaux 2005).

DILI can elevate serum levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) from injured liver cells associated with high bilirubin serum levels; or increased serum levels of alkalinephosphatase (ALP) and slightly elevated levels of ALT. DILI is the most frequent reason cited for the withdrawal of approved drugs from the market (Aithal *et al*. 2011). Depression is a mental disorder that affect the mood. Patients present lost interest in activities, decreased ability to feel pleasure, decreased energy, feeling of guilt or decreased self-esteem, sleep, appetite and concentration disorders and anxiety. Depression affects 322 million people worldwide mostly women (WHO 2017). The use of antidepressants is one of the effective strategies used to treat patients with depression. However, in patients with liver failure, treatment with antidepressants requires attention, since many drugs are metabolized by the liver and their

adverse reactions are dose-dependent (Mauri *et al*. 2014). Furthermore, antidepressants are linked to a higher risk of hepatotoxicity. DILI seems to be more frequently associated with MAO inhibitors and tricyclic or tetracyclic antidepressants (Voican *et al*. 2014) and less frequently by SSRIs (Friedrich *et al*. 2016).In this way, adequate antidepressant therapeutic management becomes a challenge in liver failure. Liver dysfunction can reduce the hepatic clearance of drugs or bile excretion and affect the binding to plasma proteins (BPP), altering the distribution and elimination process. An incomplete metabolization increase the elimination half-life of the drugs (Verbeeck and Musuamba 2009). Therefore, knowledge of the pharmacokinetic characteristics of antidepressants is desirable for the adequate indication of drug therapy for depression in patients with liver failure. Here, we aimed to determine what are the best choice to treat depression in liver disfunction based in the pharmacokinetics.

METHODS

We used articles published from January 1999 to 2021, covering searches in the databases Pubmed, Scielo, Science Direct, Springer Link, Google Scholar, Capes Periodicals, and Drugs, using the health descriptors: antidepressants, liver failure, and pharmacokinetics. Drugs database and textbooks were also consulted.18 antidepressants were selected for this review.

RESULTS

Cognitive-behavioral psychotherapy, interpersonal psychotherapy and the use of antidepressant are strategies to treat the disease. There are several classes of antidepressants with different pharmacokinetic characteristics (Table 1). As for effectiveness, antidepressants are more effective than placebo. SNRI have an efficacy comparable to ADTs and possibly greater than SSRIs (Bourin 2012; Amaral 2014). (Cipriani *et al*. 2018) reports that in terms of acceptance, only agomelatine and fluoxetine were associated with less abandonment than placebo. In comparative studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were the most effective, while fluoxetine, fluvoxamine, reboxetine and trazodone were the least effective. Citalopram, escitalopram, fluoxetine, sertraline and vortioxetine were more tolerable, while amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone and venlafaxine had higher dropout rates.

DISCUSSION

Some drugs exhibit a more suitable pharmacokinetics profile to be used in the liver injury due the higher percentage of elimination in the unchanged form in the urine, namely citalopram (about 10%) and desvenlafaxine (45%). Despite that, citalopram, fluoxetine, paroxetine, sertraline and fluvoxamine are SSRIs mostly linked with hepatotoxicity (Todorović Vukotić *et al*. 2021). Life-threatening or severe DILI has been reported for phenelzine, imipramine, sertraline, venlafaxine and duloxetine, and trazodone, while citalopram and fluvoxamine are characterized by lower risk (Todorović Vukotić *et al*. 2021). The maximum daily dose of 20mg of citalopram has been established for patients with liver failure. Although escitalopram is also metabolized by the liver and has a small percentage of the drug eliminated unchanged in the urine, a dose reduction to 5mg and a maximum of 10 mg daily is indicated in patients with mild and moderate liver dysfunction (Joubert *et al*. 2000). Desvenlafaxine, a synthetic form of the active metabolite of venlafaxine, can be considered as the best option in the treatment of patients with liver failure, because it is the drug with the highest percentage eliminated in the urine in an unchanged form. Even so, there is indication for dose adjustment or an increase in the dose interval in these patients. The usual maximum daily dose, 200mg, should be decreased to 100mg in patients with liver failure (Bhatia *et al*. 2009). A case report of a patient with Gilbert's syndrome, longstanding social phobia, and depressive disorder showed elevated liver transaminases when prescribed both duloxetine and venlafaxine. Subsequently, the patient received desvenlafaxine and had no liver abnormalities (Feinberg 2010). The metabolization of desvenlafaxine included glucuronidation, oxidation, and *N*-demethylation. In mice, rats, and dogs, desvenlafaxine-*O*-glucuronide was the most detected in plasma and urine. Urine was the primary route of excretion of desvenlafaxine in all species. Oxidative metabolism via the CYP3A4 was a minor contributor to desvenlafaxine metabolism and the drug did not induce or inhibit CYP3A4 activity suggesting that desvenlafaxine has a simple metabolic profile. Desvenlafaxine is unlikely to contribute to clinically significant CYP-mediated drug-drug interactions (Demaio *et al*. 2011). Venlafaxine is metabolized by the liver, has active metabolites and about 5% of the drug is eliminated unchanged in the urine. Higher doses require monitoring for signs of toxicity. Venlafaxine and duloxetine are associated with hepatotoxic side-effects (Todorović Vukotić *et al*. 2021). Hepatic tissue is the main responsible by drug metabolism due the presence of cytochrome P450-dependent monooxygenase (CYP) family (Furge and Guengerich 2006). The majority of antidepressants are substrates of CYP450 family, especially CYP3A4 (Zanger and Schwab 2013), in this way they have a higher probability of causing DILI in a dose-independent manner (Yu *et al*. 2014). In addition to the hepatotoxic potential of antidepressants there are specific characteristics of the patients, such as obesity and diabetes mellitus, which represent risk factors for DILI (Luppino *et al*. 2015). Lipophilic properties allow the drug to cross the cell membranes and to suffer extensive metabolism decreasing the bioavailability (Javaid 1994). During antidepressant treatment 5.1 % of the patients had elevated serum transaminase levels (Voican *et al*. 2014; Ueberberg *et al*. 2020). Some antidepressants demonstrate idiosyncratic, unpredictable, and reversible hepatic injury. The injury may onset as early as after several days or after up to 6 months after drug administration and generally ends after the drug is withdrawn (Todorović Vukotić *et al*. 2021).

All antidepressants present high degree of metabolization, and little is the percentage eliminated in the unchanged form. Some metabolites do not have their elimination percentages in the consulted literature. The information is not fully complete as is the case of tranylcypromine. Tranylcypromine/and its metabolites are renally excreted (Frieling and Bleich 2006). The metabolites are described as phase 1, but the percentual eliminated unchanged is not described. The extensive metabolism is confirmed by the low percentage of drug eliminated in the urine in the unchanged form: moclobemide < 1% (Bonnet 2002), seleginine 0.1% (Micromedex 2021), amitriptyline 5% (Gupta *et al*. 1999; Mauri *et al*. 2014), clomipramine 0.8 to 1.3% (Drugs 2019a), nortriptyline 2% (Marsh 2007), imipramine 5% (EMC 2020a), citalopram 10% (Joubert *et al*. 2000), escitalopram(FDA 2017), fluoxetine 2-5% (Altamura *et al*. 1994; Lochmann and Richardson 2019), fluvoxamine3% (Figgitt and McClellan 2000; Mauri *et al*. 2014), paroxetine 2% (Wagstaff *et al*. 2002; Mauri *et al*. 2014), sertraline 5% (Muijsers *et al*. 2002b), venlafaxine 5% (Schoretsanitis *et al*. 2019), desvenlafaxine 45% (Bhatia *et al*. 2009), duloxetine 1% (Bymaster *et al*. 2005; Drugs 2019b), DRUGS, 2019**),** trazodone 0.13% (Micromedex 2021), mirtazapine1% (Holm and Markham 1999; Moreno *et al*. 1999), bupropion 1% (Moreno *et al*. 1999; Stahl *et al*. 2004; Jefferson *et al*. 2005). SSRIs are less likely to contribute to DILI development compared to other classes of antidepressants (Friedrich *et al*. 2016). Billioti de Gage *et al*. (2018) (Billioti de Gage *et al*. 2018) not find evidence that SNRIs have a higher risk of serious liver injury than SSRIs. However, duloxetine (SNRI) showed in pre and post marketing as a causative agent of liver injury (Desanty and Amabile 2007) and thereby it had not been prescribed to patients susceptible to DILI (e.g., elderly, obese patients, individuals with diabetes, chronic renal failure, etc.). SSRIs are less likely to precipitate DILI comparing to ADTs and MAOIs, but not comparing to SNRIs. Paroxetine had the largest number of DILI cases within the SSRI class (Azaz-Livshits *et al*. 2002). The ADTs and MAOI are capable of producing hepatotoxicity, but fewer cases have been reported. Most antidepressant have the potential to produce idiopathic liver injury. The idiopathic cannot prevent, but the severity may be minimized with agent's withdrawal (Desanty and Amabile 2007).

Table 1. Pharmacokinetic characteristics of antidepressant drugs

Class	Drug / Commercial presentation	Reference	Dose	BD	Ingestion	LPP	Phase I or II metabolism Active / inactive metabolites	Elimination half-life and pathways	Dose adjustment in LD	Class action mechanism
MAOI	Moclobemide/ 150, 300 mg / TB	(Bonnet 2002)	300 - 600 mg/ day Fractional dose	40% (50 mg), 86% (200 mg), 100% (300 - 600 mg)	Fasting	50%	20 metabolites, 1 active	2 - 4 h, renal < 1% unchanged form	To reduce by half or one-third	Inhibit the monoamine oxidase (MAO) enzyme subtypes A and B involved in the metabolism of 5-HT, NA and dopamine, increasing the concentrations of these neurotransmitters in the CNS (Moreno *et al*. 1999)
MAOI	Seleginine/ 5 mg/ TB	(Micromedex 2021; Moore and Saadabadi 2021)	5 - 10 mg/ day into 2 doses	10%, increase with food	Fed	95% (strongly to erythrocytes)	Phase I	10 h, 85% urine (0.1% unchanged) 2 - 15% feces Seleginine and 3 metabolites are eliminating in 18 to 25h	Adjust in mild and moderate Not recommended in severe	
MAOI	Tranylcypromine/ 10 mg/ TB	(Preuss 2016; Ulrich *et al*. 2017)	20 mg/ day Fractional dose	50%	Fasting	NF	Phase I, not active	1.5 – 3.5 h, renal	Not use	
ADTs	Amitriptyline/ 10, 25, 75 mg/ TB	(Gupta *et al*. 1999; Mauri *et al*. 2014)	75 mg/ day Fractional dose	45%	Fasting or Fed	85 - 95%	Phase I and II, 4 metabolites active	9-25 h, renal as phase I or II metabolites and 5% unchanged	Caution in patients with LD	Acting in the pre-synaptic cleft blocking the recapture of amines as NE and 5-HT and, to a lesser extent dopamine, through competition for the binding site of the amine transporter. ADTs also block postsynaptic cleft including M, H1, 5HT2 and α2 adrenergics receptors. Antimuscarinic effects contribute to the side effects (Rang and Dale 2016)
ADTs	Clomipramine/ 25 mg/ TB	(Drugs 2019a)	25 mg, 2 to 3 times/ day	50%	Fasting or Fed	9%	Phase I active, phase I and II inactive	19-37 h drug, 54-77 h demethyl-clomipramine metabolite Urine (50% to 60%; 0.8% to 1.3% unchanged and active metabolite; feces (24% to 32%)	Caution in patients with LD	
ADTs	Imipramine/ 10, 25 mg/ dragee	(Mauri *et al*. 2014; EMC 2020a)	25 mg, 1-3 times/ day	22-95%	Fasting or Fed	60 - 96%	Phase I, active Mainly by demethylation and hydroxylation	About 19 h, 80% urine mainly as metabolites (inactive), active desmethylimipramine metabolite (6%), unchanged (5%), 20% feces	Monitor the patients	
ADTs	Nortriptyline/ 10, 25, 50, 75 mg/ CAPS	(Marsh 2007)	10 to 50 mg, 3 to 4 times/ day	51%	Fasting or Fed	85 - 95%	Phase I, active	15 -39 h, 62% urine as metabolites and unchanged (2%), also some % via feces	Caution in patients with LD	

Continue ….

SSRI	Citalopram/ 20, 40 mg/ TB	(Joubert *et al*. 2000)	20 or 40 mg in a single dose	79%	Fasting or Fed	79%	Phase I, 3 actives, 1 inactive	1.5 days, 10% unchanged in urine, 5% metabolites, 85% via feces	Do not exceed 20mg / day and to monitor the patients	Act on the presynaptic neuron selectively inhibiting 5-HT reuptake, potentiating serotonergic neurotransmission. The increase in the availability of 5-HT stimulates postsynaptic 5-HT receptors related to the adverse effects, including decreased libido and gastrointestinal effects (Silva and Andrade 2008)
SSRI	Escitalopram/ 10, 15, 20 mg/ CT	(Murdoch and Keam 2005; DrugBank 2017; FDA 2017; EMC 2020b; PubChem 2021)	10, 15 or 20 mg / day	80%	Fasting or Fed	Near to 55%	Phase I, active demethylated escitalopram, N-oxide metabolite Phase II, inactive	27 to 33 h, via urine as metabolites (28-31% demethylated and <5% didemethylated), 10% S-demethylcitalopram and 8% unchanged, and also eliminated via feces	5mg / day, can be increased to 10mg/ day in mild and moderate, caution in severe	
SSRI	Fluoxetine/ 10, 20 mg/ CAPS or CT	(Altamura *et al*. 1994; Lochmann and Richardson 2019)	20mg/ day	72%	Fasting or Fed	94%	Phase I active, other metabolites	1 to 4 days for fluoxetine and 7 to 15 days for main metabolite 80% urine, 2-5% unchanged, 15% feces	Reduce dose or increase interval	
SSRI	Fluvoxamine/ 50, 100 mg/ TB	(Figgitt and McClellan 2000; Mauri *et al*. 2014)	50 to 100 mg/ day (in the evening)	50%	Fasting or Fed	77%	11 metabolites, inactive	17 - 22 h Urine as metabolites (two major metabolites are inactive), about 3% unchanged	Reduce doses, increase dose range, to monitor the patients with moderate and severe	
SSRI	Paroxetine/ 10, 12.5, 20, 25, 40 mg/ CT	(Wagstaff *et al*. 2002; Mauri *et al*. 2014)	10-50 mg/ day (in the morning)	About 50%	Fasting or Fed	95%	Phase I and II, inactive	21 h, 62% urine, 36% feces, 2% unchanged	10 mg/ day and not to exceed 40 mg/ day	
SSRI	Sertraline/ 50, 100 mg/ CT	(Muijsers *et al*. 2002a)	50 mg/ day Maximum daily dose: 200mg	44%	Fasting or Fed	98%	Phase I, active (less activity than drug)	26 h for sertraline, 6-104 h for main metabolite, 5% unchanged in urine, is also eliminated via feces	Reduce dose or increase interval	
SNRI	Venlafaxine / 37.5, 75, 150 mg/ CAPS extended release	(Schoretsanitis *et al*. 2019)	75 to 150 mg/ day Fractional dose. 350 mg/ day maximum dose in severe cases.	40-45%	Fed	27% drug 30% ODV	Phase I actives called ODV and NDV (less active), other Phase II	5 h for venlafaxine, 55% as ODV (29% unconjugated ODV, 26% conjugated ODV), 27% as other metabolites, about 5% unchanged.	Reduce total daily dose by up to 50% or more in mild or moderate	Analogous to ADTs, with greater tolerability, without affinity for M, H1, α1- adrenergics, opioids or GABAergics receptors responsible for side effects. They inhibit both 5-HT and NE uptake, increasing serotonergic and noradrenergic neurotransmission and have weak dopamine reuptake inhibitory activity (Moreno *et al*. 1999; Bourin 2012)
SNRI	Desvenlafaxine/ 50, 100 mg/ CT	(Bhatia *et al*. 2009)	50 mg/ day, not to exceed 200 mg/ day	80%	Fasting or Fed	30%	Phase I and II	11 h, 45% unchanged in urine, 19% as a glucuronide metabolite, 5% as other metabolites	No dose adjustment is necessary. Do not exceed 100mg/ day	
SNRI	Duloxetine/ 30, 60 mg/ CAPS	(Bymaster *et al*. 2005; Drugs 2019b)	60 mg/ day, not to exceed 120 mg/ day	30-80%	Fasting	96%	Phase I and II	12 h, 20% in feces, 70% in urine as metabolites and 1% unchanged	Not use	
AR 5HT	Mirtazapine/ 15, 30, 45 mg/ TB	(Holm and Markham 1999; Moreno *et al*. 1999)	Initial of 15 or 30 mg/ day, can be increased to 45 mg/ day	About 50%	Fasting or Fed	85%	Phase I and II. N-desmethyl is active	20-40 h, 74% urine, 1% unchanged, 20% feces	Clearance is reduced by 30% in LD	They blocking 5HT2 and α1- adrenergic receptors. The exact mechanism is not yet clearly established (Cantarelli and Marcolin 2006)
AR 5HT	Trazodone/50, 100, 150mg/ TB	(Moreno *et al*. 1999; Cantarelli and Marcolin 2006; Micromedex 2021)	50-150 mg/ day in a single dose or in 2 times	NF	Fed	85 - 95%	Phase I, active called mCPP	5-9 h, 70% urine (0.13% unchanged), 20% feces	Monitor the use in these patients. Use with caution	
ADA	Bupropion/ 150, 300 mg/ CT	(Moreno *et al*. 1999; Stahl *et al*. 2004; Jefferson *et al*. 2005)	150 mg/ day and may increase to 150 mg twice a day	NF	Fed	84% drug 77 % Hydroxy-bupropion	Phase I, 3 actives. HB is the main	12 - 30 h, 10% feces, 87% urine, 1% unchanged	Reduce the frequency of doses, use with caution in patients with mild to moderate	Acting through multiple mechanisms not fully known. inhibit reuptake in transporters for both dopamine and NE, with slightly greater potency in the dopamine than in the NE transporter and have no affinity for postsynaptic receptors (Stahl *et al*. 2004)

5-HT – serotonin; 5HT2 - serotonin receptor; ADA- Atypical antidepressants;ADTs- Tricyclic Antidepressants; AR 5HT- 5HT receptor antagonists; BD- bioavailability; CAP- capsules;CNS - central nervous system; CT - coated tablets; H1 - histamine receptor; LD - Liver dysfunction; LPP - plasma protein binding;M - muscarinic receptor; MAOI- Monoamine Oxidase Inhibitors; mCPP - meta-chlorophenylpioerazine;NA – noradrenaline; NDV- N-desmethyl-venlafaxine;NE - norepinephrine; NF- Not found; ODV- O-desmethyl-venlafaxine;SNRIs - Serotonin and norepinephrine reuptake inhibitors; SSRIs- Selective serotonin uptake inhibitors; TB – tablets.

A case study reported asymptomatic elevation of liver enzymes after bupropion treatment which returned to normal values after bupropion stopped (Kılıç *et al*. 2017). Antidepressant affect drug-metabolizing enzymes and therefore provoke drug–drug interactions (Todorović Vukotić *et al*. 2021). Drug interactions can be of a pharmacokinetic or pharmacodynamic nature. Pharmacodynamic interactions suggest that mechanisms of actions or adverse effects are altered. Pharmacokinetic drug interactions occur when one drug alters the absorption, distribution, metabolism, or elimination (Preskorn and Werder 2006). The interactions with antidepressants predominantly involve drug-induced changes in hepatic metabolism (Bleakley 2016). The antidepressants high metabolized used with other drugs result in drug-drug interactions or when the drugs are used in patients with liver failures requiring dose adjustment. For example, the co-administration of escitalopram with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in approximately 50% of increase in the plasma concentrations of escitalopram (EMC 2020b). SSRIs have the potential to cause drug–drug interactions through inhibition of CYP. Fluoxetine and paroxetine are potent CYP2D6 inhibitors, whereas norfluoxetine, the main metabolite of fluoxetine, has a moderate inhibitory effect on CYP3A4 isoenzyme. Sertraline is a moderate inhibitor of CYP2D6, while citalopram has little effect on the major CYP isoforms (Hemeryck and Belpaire 2002; Todorović Vukotić *et al*. 2021).

CONCLUSION

The best antidepressant option for treating patients with depression and liver injury is desvenlafaxine. However, should be evaluated the drug's effectiveness in treating depressive symptoms. The use of other antidepressants can be considered with a possible adjustment of doses or alteration of interval dose, presence of adverse reactions and monitoring of the level of liver transaminases. The relationship between dose and effect of antidepressants can vary between patients, mainly due to pharmacokinetic differences influenced by age, changes in the first-pass effect, and the induction or inhibition of the metabolic system. All antidepressants have some degree of hepatic metabolism. The choice of the prescriber to treat patients with liver failure should consider the pharmacokinetic characteristics of antidepressants and the characteristics of metabolization, as well as the use of other drugs higher metabolized.

Declarations: Funding: Own financial support

Conflicts of Interest: There are no conflicts of interest for specific or individual authors.

Availability of data and material: Not applicable

Ethics approval: Not applicable

Consent: Not applicable

Author contributions: Conception and design: TT, CDB, KR; development of methodology: TT, CDB; acquisition of data: TT, VCS, PN, KR, CDB; analysis and interpretation of data: CDB, CMF, LGRG; writing, review, and/or revision of the manuscript: TT, KR, CMF, CDB, LGRG.

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