CHARACTERIZATION OF AGOMELATINE-INDUCED LIVER ENZYME INCREASE:

FREQUENCY AND RISK FACTORS DERTERMINED FROM A POOLED ANALYSIS OF 7,605 TREATED PATIENTS

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GP, PC, DV, DG, KM have analyzed all the suspected cases of liver injury.

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ABSTRACT

Background. Antidepressant-induced liver injury is a major concern and a liver monitoring scheme has been recommended by the European Medicine Agency for agomelatine.

Objective. To assess the liver safety and identify the characteristics of patients who developed a significant increase in transaminases whilst taking agomaatine.

Method. A retrospective pooled analysis of changes in transaminase levels in 9,234 patients treated with agomelatine (25mg or 50mg/day; n=7,605) or placebo (n=1,629) from 49 phase II and III studies was undertaken. A significant increase in transaminase levels was defined as an increase to >3-fold the upper limit of normal (>3ULN). Final causality was determined in a case-by-case review by five academic experts.

Results. Serum transaminase increased to >3ULN in 1.3% and 2.5% of patients treated with 25mg and 50mg of agomelatine respectively, compared to 0.5% for placebo. The onset of increased transaminases occurred before 12 weeks in 64% of patients. The median time to recovery (to≤2ULN) was 14 days following treatment withdrawal. Liver function tests recovered in 36.1% patients despite continuation of agomelatine, suggesting the presence of a liver adaptive mechanism. No cases of acute liver failure or fatal outcome occurred. Patients with elevated transaminases at baseline, secondary to obesity/fatty liver disease, had an equally increased risk of developing further elevations of transaminases with agomelatine and placebo.

Conclusion. Incidence of abnormal transaminases was low and dose-dependent. No specific population was identified regarding potential risk factors. Withdrawal of agomelatine led to rapid recovery, and some patients exhibited an adaptive phenomenon. Overall, in clinical trials, the liver profile of agomelatine seems safe when serum transaminases are monitored.

KEY POINTS

- Incidence of agomelatine-induced transaminase increase is low and dose-dependent.

- Withdrawal of agomelatine leads to rapid recovery.

- Some patients exhibit an adaptative phenomenon.

- The liver profile of agomelatine seems safe when serum transaminases are monitored.

1. INTRODUCTION

Agomelatine belongs to a new class of antidepressants. Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and serotonergic 2C (5-HT2C) antagonist. Binding studies indicate that agomelatine has no effect on monoamine uptake and no affinity for α- and β-adrenergic, histaminergic, cholinergic, dopaminergic or benzodiazepine receptors [1, 2]. Agomelatine has no addictive properties and its abrupt cessation is not associated with any withdrawal symptoms [3].

Agomelatine was approved by the European Medicines Agency (EMA) in 2009 for treatment of major depressive episodes in adults [1]. The safety of agomelatine was assessed in a large number of phase II and phase III studies conducted by Servier and its US partner and included more than 14,000 patients. The most frequent adverse events include, by rank of frequency, headache, nausea, dizziness, somnolence, diarrhoea and dry mouth.

Spontaneous reports of increase in liver transaminases have been reported in agomelatine-treated patients. A liver monitoring scheme has been therefore recommended by the European Medicine Agency (EMA). Liver function tests should be performed before starting treatment and then after around 3 weeks, 6 weeks (end of acute phase), 12 and 24 weeks (end of maintenance phase), and thereafter when clinically indicated. When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment. Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours. Agomelatine should be discontinued if the increase in transaminase exceeds 3 fold the upper limit of normal value (3ULN) [1].

Currently EMA and the MAH recommend that agomelatine is administered after careful consideration of benefit risk in patients with pre-existing liver diseases including fatty liver, obesity, diabetes, substantial alcohol intake or concomitant use of drugs with hepatotoxic potential. The scheme of liver monitoring and the data supporting the use of such criteria are

lacking. Of note, such data are also lacking for the other antidepressant. It is therefore difficult to draw conclusions about the prevalence, the severity the risk factors of antidepressant-induced liver injury.

In this context of monitoring agomelatine-induced liver enzyme increase, we aimed to examine the incidence and characteristics of transaminase increase in patients treated with agomelatine who participated in phase II and III clinical trials.

2. METHODS

2.1. Patients

A retrospective pooled analysis of the hepatic safety of agomelatine was assessed in 14,377 patients participating in all phase II and III trials conducted either by Servier or its US partner and completed by end 2013. The data come from 35 completed studies in major depressive disorders (N=12,307) and 14 completed studies for other indications (N= 2,070). Among 49 clinical studies, 28 are published [2, 4-30], 3 are submitted for publication, and the other were used for the European registration file. All studies were assessed by the EMA. All these studies included 7,605 patients treated with agomelatine (25-50mg) and 1,629 patients treated with placebo, and importantly this analysis only included patients in whom there was at least one post baseline value of transaminase. In the present analysis, in order to be able to extend our results to marketed doses of agomelatine, we focused our study to patients treated with 25 and 50 mg daily. We therefore excluded patients treated with other antidepressant, non-marketed doses of agomelatine (1, 5, 10 and 100 mg) and patients for whom no information regarding transaminase levels under treatment was available (Figure 1). This left 9,234 patients treated with agomelatine or placebo for analysis.

For the purpose of this analysis, an increase of transaminase was defined as significant when there was at least one value of ALT or AST>3ULN on treatment. The 3 fold ULN of transaminase is based on internationally recognised Guidance of DILI [31]. Of note, as transaminase dosage is highly variable among tests, we considered the upper limit of normal the value that was given by the laboratory for each test.

2.2. Assessment of the causal relationship

A Liver Safety Committee (LSC) which comprised five academic experts (4 hepatologists and 1 internist) was set up by Servier to monitor liver safety in agomelatine-treated patients. A

blinded case-by-case review was performed by the LSC. Experts were asked to classify all the cases to one of 4 classes of causality. These were 1) Probably related to the study treatment, 2) possibly related to the study treatment, 3) unlikely related to study treatment or 4) not related to study treatment (levels 1 to 4). 1) "Probably related" to the (study) treatment was used when the transaminase increase was clearly suggestive of a drug-related reaction in the absence of known confounding factors or in the presence of confounding factor(s) but less likely to have caused the event than the study drug; 2) "Possibly related" to the (study) treatment, as compatible with a drug-related reaction, in the absence of known confounding factors or in the presence of confounding factor(s) but not more likely than the study drug to have provoked the event; 3) "Unlikely related" to the (study) treatment, as compatible with a drug-related reaction, but with the presence of one or more confounding factors considered to be more likely than the study drug to have caused the increase in serum transaminase and/or an unusual pattern for a drug-induced reaction; 4) "Not related" to the (study) treatment, as clearly incompatible with a drug-related reaction and/or another cause (e.g acute hepatitis E) has been identified. In addition, a fifth causality category 5) Unknown: was used only for the first cases occurring before 2008 in placebo-treated patients (N=7) and reviewed a posteriori in an unblinded condition.

When there was no consensus of causality attributed to a patient, a consensus was achieved during a face to face meeting. Further, whenever an expert assigned causality as "probably related" the case was discussed face to face by all experts. In the few cases when consensus was not achieved, the highest level of causality was attributed.

During the initial assessments, and once the drug administered was un-blinded, it became apparent that some patients developed an increase in transaminase which improved despite continuation of treatment. It therefore became evident that some patients exhibited what is now known as an adaptive phenomenon, enabling improvement or recovery despite continuation of treatment.

Hy's law criteria were used to identify patient that could go on to develop acute liver failure: increase of ALT or AST higher than 3 ULN together with an increase of bilirubin higher than 2 ULN, in the absence of cholestasis and excluding those patients in whom an alternative cause was evident [31].

2.3. Statistical analyses

Baseline descriptive statistics are provided for all patients: 7,605 treated with agomelatine 25/50 mg/d and 1,629 placebo. Homogeneity of the distribution of the baseline characteristics are assessed using Student's T-test for continuous variables and Pearson's Chi-square test for categorical variables.

Time to onset (i.e the number of days between first intake of agomelatine and the initial significant transaminase abnormality (>3ULN)), outcome and time to recovery were studied in patients assigned to being "probably or possibly related" only. Recovery was defined as a return to normal values or values lower than those observed before the first intake of agomelatine, as being≤2ULN. Patients were considered as recovering when transaminase decreased to a level<3ULN.

Unadjusted Cox proportional hazard models were used to estimate the effect of each potential risks factor, 95% CI and associated *P*-value in both the agomelatine and the placebo groups to confirm the identification of the potential risk factor.

Treatment effect from unadjusted Cox proportional hazard models, 95% CI and associated *P*-value were provided by subgroup. *P*-value for interaction between treatment group and subgroup status was obtained by addition of interaction term of treatment and subgroup in the model.

3. RESULTS

3.1 Patient's characteristics

Baseline characteristics of the 7,605 patients on agomelatine 25-50 mg/d and the 1,629 patients on placebo are reported in Table 1. At inclusion, there was a higher number of patients with a BMI>30 kg/m² in the agomelatine group (22.56 %) than in the placebo group (19.52 %). However, the prevalence of high blood pressure, increase of AST, GGT and blood glucose was higher in the placebo group (Table 1). Of note, 7.76 % of patients in the agomelatine group and 8.35 % in the placebo group had a baseline level of ALT higher than the upper limit of normal.

There were 139 patients with an increase of transaminase>3 ULN. Of these, 131 (1.7%) patients were taking agomelatine (25 or 50 mg/d) (Table 2), and 8 patients placebo (0.5%). Of the 131 patients with an increase of transaminase>3 ULN on agomelatine, 21 cases were assigned as probably related, 65 cases as possibly related, 32 cases as unlikely related and 13 cases were considered unrelated to agomelatine (Figure 1).

3.2. Incidence of increased transaminases > 3ULN

The pooled incidence of increased serum transaminases to >3ULN in the 9,234 patients analysed was 1.3% and 2.5% in patients treated with 25 mg and 50 mg/d of agomelatine respectively (25 mg vs 50 mg/d, $p<0.001$), compared to 0.5% in placebo-treated patients (agomelatine 25 mg or 50 mg/d vs placebo, $p<0.001$).

Twenty patients (0.3%) taking agomelatine exhibited a marked increase of transaminase>10 ULN (Table 2). Of these 20 patients, none had severe liver injury defined by the Hy's law criteria. One patient had an increase of bilirubin level on agomelatine treatment at 62 µmol/L. However, this case was classified as unlikely related to agomelatine due to the chronology of the event and a concomitant treatment with itraconazole. No cases of acute liver failure or fatal outcome were reported from the clinical trials.

3.3. Analysis of cases assigned as "possibly" or "probably related"

When patients classified as "possibly or probably related" were analyzed, the observed frequency of increased transaminases was 0.8% and 1.7% with 25 mg and 50 mg/d of agomelatine, respectively, versus none on placebo (25-50 mg/d vs placebo $p \leq 0.001$) (Table 2). Of these patients, a daily dose of 50 mg agomelatine was associated with a higher proportion of patients with serum transaminase increase >10 ULN (0.3 %) compared to 25 mg/d (0.1%) (p=0.075) (Table 2). Overall, these data show a dose-relationship with a dose of 50 mg agomelatine/d being associated with a more frequent incidence of serum transaminases to>3ULN.

We also assessed the time between the first intake of agomelatine and the first occurrence of transaminase increase>3ULN. The time to onset of increased serum transaminase > 3ULN occurred within the first 12 weeks of treatment in 64% of patients classified as "possibly or probably related to agomelatine" (Figure 2A). In 8.1% of patients classified as "possibly or probably", the onset of transaminase increase occurred after 24 weeks of treatment.

3.4. Outcome and liver adaptation

All of the patients with an attributed possibly or probably agomelatine-induced transaminase increase for which a follow-up was available (96% of cases) recovered or were recovering. Three patients classified as "not recovered" had a limited follow up in time; in these patients, no significant change between maximum and last available transaminase value was notified. The median time to recovery was 14 days following treatment withdrawal.

One striking observation was that many agomelatine-treated patients had an improvement or a normalization of transaminase level despite continuation of treatment. This phenomenon is called adpatation. Indeed, among the 86 patients in who the increase in serum transaminase>3

ULN was attributed to being possibly or probably related to agomelatine, 31 (36.1%) cases demonstrated continued improvement or recovery despite continuation of agomelatine. Recovery of the transaminitis despite continuation of agomelatine was observed at both 25 mg/d (15 patients) and 50 mg/d (16 patients). The time between the first increase in serum transaminases and the first intake of agomelatine also occurred in the majority of patients with adaptation within the 12 first weeks of treatment (Figure 2B). The only difference found between patients with and without adaptation was a higher baseline level of GGT in patients without adaptation (Table 3).

3.5. Risk factors for an increase in serum transaminases > 3ULN

The EMA has recommended that patients with pre-existing fatty liver disease (non-alcoholic fatty liver disease, NAFLD) are treated with agomelatine after careful consideration of benefit risk. In this context, we analysed factors that might be associated with significant increases in transaminase >3ULN. Sex and age were not associated with a risk of transaminase increase (Table 4). However, the presence of a baseline level for AST, ALT, GGT or triglyceride above the upper limit of normal, as well as metabolic syndrome mainly driven by obesity and elevated cholesterol was significantly associated with a higher risk to develop an increase of serum transaminase>3ULN in patients treated with agomelatine. In patients on placebo, a baseline level higher than the reference range for ALT and GGT was also associated with an increased risk of transaminase elevation>3ULN (Table 4). However, since the diagnosis of NAFLD relies on a fluctuation of transaminases between 1 to 3 ULN, the observation of an increase of transaminase in patients treated with agomelatine may be difficult to interpret. Therefore, to test whether NAFLD could be a risk factor of agomelatine-induced transaminase increase, we analysed whether an increased baseline of transaminase was associated with a higher risk of developing an elevation of transaminase higher than 3 ULN. Patients with an

increased baseline of transaminase were more at risk to developed a serum transaminase higher than 3ULN than patients with a normal baseline in both the placebo group (2.55% vs 0.27%), and the agomelatine group (3.41% vs 1.56%) (Table 5).

Patients with normal baseline transaminases had a higher risk of developing an increase of transaminase on agomelatine than on placebo (1.56% vs 0.27%; $p<0.05$) (Table 5). However, in patients with elevated baseline transaminase, the incidence of transaminase increase during treatment was not statistically different between agomelatine and placebo-treated patients (Table 4). These results suggest that the presence of a baseline elevation of transaminases, probably related to NAFLD, is not an additive risk of agomelatine-related transaminase increase.

To distinguish between NAFLD and a more likely drug-induced liver injury in patients with a transaminase increase, we assumed that an increase of transaminases to >5 or 10ULN under treatment was more likely related to agomelatine rather than to the fluctuation of transaminases observed in NAFLD. We therefore compared the risk of transaminase increase>5 and 10ULN between patients with normal or increased baseline level of transaminases (Table 5). Again, there was no evident additive effect on the risk of ALT >5 or 10ULN under agomelatine treatment, in patients with an increased baseline level of ALT or AST (for 5 ULN: 1.34 % vs 0.78%; for 10 ULN: 0.15% vs 0.27 %) (Table 5).

Overall, these analyses suggest that a baseline elevation of transaminases, usually related to NAFLD, is not a risk for agomelatine-induced liver injury.

4. DISCUSSION

This review of the cases of agomelatine induced hepatotoxicity as defined by a serum transaminase increase>3ULN in phase II and III clinical trials shows that incidence of transaminase increase was low and dose-dependent being 2.5% at a dose of 50 mg/day vs 1.3% at 25 mg/day. The majority of increases in serum transaminase occurred within the first 3 months of treatment, and in particular between the forth and the twelfth weeks after the first intake of agomelatine.

Antidepressant-induced liver injury remains a rare event [33]. In a retrospective analysis of duloxetine safety in 23,983 subjects, an increase of ALT was observed in 13% of patients, 12.7% of them (1.7% of total) having a value higher than 3ULN [34]. A study on venlafaxine safety that included 3000 patients showed an incidence of elevated transaminase levels (3ULN) of 0.4% [35]. Of note, in these studies, as well as the present analysis, the increase of transaminase was not necessarily related to the drug itself but may be due to many other causes including alcohol misuse, fatty liver disease, or viral hepatitis etc...

We have tried to identify risk factors for transaminase increase in agomelatine-treated patients. Usually, female sex [36, 37] and older age [38] are considered as risk factors for DILI. We did not find such associations for agomelatine. We found that baseline serum transaminase greater than the upper limit of normal was associated with an increased risk of observing a serum transaminase>3ULN, in both agomelatine- and placebo-treated patients. These data were confounded by the fact that patients taking placebo were treated and monitored for 100 days with an average of 1.8 (± 0.9) tests per patient, whereas those taking agomelatine were treated for 160 days, with an average of 3.1 (± 3.5) tests/patient. Increased frequency of transaminases measurement is known to be associated with an increased incidence of transaminase elevation in placebo treated patients [32]. Non-alcoholic fatty liver disease (NAFLD) is the liver manifestation of the metabolic syndrome (REF PERLEMUTER). NAFLD is therefore

associated with overweight, insulin resistance, diabetes and dyslipidemia. NAFLD may progress from pure steatosis (fatty liver) to steatohepatitis, fibrosis and cirrhosis. Prevalence of NAFLD is high, about 23% of the general population, and increases to 74% among obese individuals [39]. Serum transaminase in patients with NAFLD can vary and be as high as 8-10 ULN, but in most patients levels vary from to 1 to 4ULN. Our patients exhibited a relatively high prevalence of either being overweight (~31%) or obese (~22%) and ~9% had an elevated baseline serum transaminase, consistent with a high prevalence of NAFLD. Patients with NAFLD frequently exhibit marked variations in serum transaminase. Thus, it is to be expected that if you treat patients with NAFLD with any drug that some will show an increase in transaminase just by chance and unrelated to the study medication. Our results show an increased risk of developing an increase in transaminase>3 ULN in patients with probable NAFLD with both agomelatine or placebo, however, the number of placebo cases are relatively small making an accurate assessment impossible. Therefore, we considered in other analyses that an elevation of transaminases to>5 or 10 ULN was more likely to be related to agomelatine rather than to fluctuation in NAFLD. In these analyses, a baseline increase of transaminase was not a risk factor for an agomelatine-associated transaminase increase. Thus, in our view, although the data are clear, that is if you have elevated liver enzymes at the start of treatment, you are more likely to show an increase in serum transaminase>3 ULN, we do not believe that NAFLD is an actual risk factor for agomelatine hepatoxicity.

We observed a dose-dependent risk of transaminase increase, the pooled incidence of transaminase increase being 1.3 % and 2.5 % for a daily dose of 25 mg and 50 mg of agomelatine, respectively. Idiosyncratic hepatotoxicity is classically known to occur without obvious dose-dependency and in an unpredictable fashion [40]. Nevertheless, 50 mg/d of drug intake has been indeed suggested to be a threshold of an increased risk of transaminase [41]. No cases of severe liver injury, defined by the occurrence of coagulopathy or any degree of

encephalopathy or jaundice, of acute liver failure or of fatal outcome were observed. Of note, all the patients with available follow-up recovered or were recovering. The most specific predictor found to date of a drug's potential for severe hepatotoxicity is the occurrence of a small number of cases of hepatocellular injury accompanied by increased serum total bilirubin (Hy's law [42]). No cases of Hy's law have been observed in agomelatine phase II and III studies. Another signal is the presence of an increase of transaminase>10 ULN. In the present study, 0.2 % of patients with increased transaminases classified as possibly or probably related to the treatment displayed such an increase. Among them, all recovered including one who recovered despite continuation of agomelatine.

One striking observation of this study was that many agomelatine-treated patients recovered despite continuation of treatment. The phenomenon of transaminase normalisation despite continuation of a treatment has been called adaptation [43]. It involves genes of drug metabolizing enzymes and transporters. Many elevations of ALT during intake of potentially hepatotoxic drugs may resolve with continued therapy. This adaptation has been clearly demonstrated with isoniazid [review in [44]]. With these drugs, patients may exhibit a very high increase of ALT that can resolve completely despite maintenance of treatment. Although adaptation may occur with other drugs, this phenomenon is probably underestimated since the drug is frequently stopped when serum transaminase increases. The explanation for the reversible ALT elevation is not known. One possibility is that there is no relationship at all to liver injury capable of progressing to liver failure [45]. Another possibility is that patients who are unable to develop adaptation are those that tend to develop severe liver injury or even acute liver failure. In line with this hypothesis is that the ALT elevation observed in patients with and without adaptation occurred both in the majority of patients in the 12 first weeks of treatment. Of note, it is unlikely that a transient elevation of transaminases should have any long-term health consequences if adaptation occurs [45].

There are clear limitations to the present study. The main limitation is the well-known low ability of clinical trials to evaluate the association between a treatment and a liver injury as this adverse event is rare. Clinical trials are of short duration and may exclude patients with pre-existing potential risk factors for liver injury. The number of patients taking placebo was low. Therefore, the number of patients may be too low to clearly identify independent risk factors, if any, for transaminase increase. We have not studied other possible risk factors such as co-administration of other drugs, smoking, oral contraception or chronic viral hepatitis. The experts of the LSC of agomelatine have reviewed, in addition to the present cases from clinical trials, 390 spontaneous notifications of suspected agomelatine-induced liver injury. Many of these were difficult to assess as data were scarce. However, among these cases representing an estimated patient exposure of 13,277,836 patient-months, two cases have been associated with acute liver failure which were assessed as being probably related to agomelatine: in one case, the patient recovered after withdrawal of agomelatine and irbesartan, (the other suspected drug for liver failure) (unpublished case). In the other case, the outcome was favourable after a liver transplantation [46]. Of note, there was no follow-up of liver enzymes during agomelatine treatment in this case.

The comparison of liver toxicity between antidepressant is difficult: data are scarce and no comparative trial focusing on this specific aim has been published. Cases of fulminant hepatic failure leading to liver transplantation or death, have been reported for other antidepressants, including phenelzine, imipramine, amitriptyline, venlafaxine, duloxetine, sertraline, bupropion, trazodone) (review in {Voican, 2014 #1241}). Current data suggest that all antidepressants may be associated with a risk of hepatotoxicity. However, the number of reported cases of DILI is inevitably higher for the most frequently used antidepressants, which may tend to indicate, falsely, a higher hepatotoxicity rate. By contrast, is impossible to precisely report prevalence and severity of antidepressant-induced liver injury {Gartlehner, 2008 #1384}.

Nevertheless, it has been suggested that the incidence of antidepressant-induced liver toxicity requiring hospitalisation is 1.28-4 cases per 100,000 patient-years, except for nefazodone, for which the incidence can be estimated to be 29 cases per 100,000 patient-years {Cooper, 1988 #1386;DeSanty, 2007 #1385} .

5. CONCLUSION

In phase II and III trials, agomelatine is associated with a significant but relatively low risk of elevated serum transaminase>3ULN which may be increased in patients with fatty liver. It has been suggested that there is no advantage on depressive symptoms to increase the daily dose of agomelatine from 25 to 50 mg (BMJ metaanalyse). As we found a dose-dependence for agomelatine-induced transaminase increase, we also recommend the use of a daily dose of 25 mg rather than 50 mg daily. No severe hepatic events were detected. In clinical practice, the regular monitoring of liver function tests is mandatory to identify patients with agomelatine-related hepatotoxicity. A baseline test of transaminases, prior to the first intake of agomelatine, will identify patient with an underlying liver disease. Such a test will also allow identifying retrospectively patients with an agomelatine-related liver enzyme increase. Overall the liver profile of agomelatine seems safe when serum transaminases are monitored.

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7. TABLES

Table 1. Baseline characteristics of patients

			Agomelatine 25-50 mg	Placebo	P-value*
Number of patients			7,605	1,629	
Age		Mean (±SD)	45.4 (±13.8)	48.2 (±16.5)	<0.001
Gender	Female	n (%)	5230 (68.77)	1113 (68.32)	0.724
BMI (kg/m²)		Mean (±SD)	26.66 (±6.29)	26.09 (±5.64)	<0.001
	<18.5	n (%)	269 (3.54)	56 (3.44)	
	[18.5-25[	n (%)	3234 (42.52)	721 (44.26)	
	[25-30[	n (%)	2355 (30.97)	527 (32.35)	
	≥30	n (%)	1716 (22.56)	318 (19.52)	
Weight (kg)		Mean (±SD)	74.42 (±19.61)	72.83 (±17.43)	0.001
Systolic blood pressure (mmHg)		Mean (±SD)	123.7 (±14.6)	125. 9 (±15.4)	<0.001
	≥130mmHg	n (%)	2693 (35.41%)	709 (43.52%)	
	<130mmHg	n (%)	4864 (63.96)	914 (56.11)	
Diastolic blood pressure (mmHg)		Mean (±SD)	76.9 (±9.3)	77.2 (±9.9)	0.208
	≥ 85mmHg	n (%)	1495 (19.66)	365 (22.41)	
	< 85mmHg	n (%)	6062 (79.71)	1258 (77.23)	
AST	> REF	n (%)	260(3.42%)	73(4.48%)	0.037
ALT	> REF	n (%)	590(7.76%)	136(8.35%)	0.422
ALP	> REF	n (%)	217(2.85%)	45(2.76%)	0.841
GGT	> REF	n (%)	735(9.66%)	185(11.36%)	0.039
Triglycerides	> REF	n (%)	1969(25.89%)	404(24.80%)	0.361
Glucose	> REF	n (%)	631(8.30%)	241(14.79%)	<0.001

(*) P-value from Student's t-test for continuous variables and Pearson's Chi-square test for categorical variables

Table 2. Incidence and importance of transaminase increase according to the classification of the Liver Safety Committee

		Classification of cases by the Liver Safety Committee		
		All cases N (%)	**Possibly or Probably related N (%)**	**Adaptative cases N (%)**
25mg (N=4,957)	>3 ULN	65 (1.3)	41 (0.8)	15 (0.3)
	>10 ULN	9 (0.2)	5 (0.1)	2 (0.0)
50mg (N=2,648)	>3 ULN	66 (2.5)	45 (1.7)	16 (0.6)
	>10 ULN	11 (0.4)	8 (0.3)	0 (0.0)
25-50mg (N=7,605)	>3 ULN	131 (1.7)	86 (1.1)	31 (0.4)
	>10 ULN	20 (0.3)	13 (0.2)	2 (0.0)
Placebo (N=1,629)	>3 ULN	8 (0.5)	-	-
	>10 ULN	1 (0.1)	-	-

Table 3. Comparison of patients with/without liver adaptation

	Adaptative cases (n=31)	Non-adaptative cases (n=108)	p
Age (years±SD)	47.6 (±11.3)	48.9 (±13.3)	0.62
Gender (female, n)	19 (61.3 %)	73 (67.6 %)	0.51
BMI (kg/m^2)	28.8 (±5.5)	28.1 (±7.3)	0.63
Systolic blood pressure (mmHg)	124.2 (±12.8)	126.6 (±14.6)	0.39
Diastolic blood pressure (mmHg)	80.2 (±7.1)	78.9 (±8.6)	0.46
AST >REF, n	1 (3.2%)	13 (12.0)	0.15
ATL >REF, n	2 (6.45%)	22 (20.4%)	0.07
ALP >REF, n	1 (3.2%)	5 (4.63%)	0.74
GGT >REF, n	3 (9.7%)	34 (31.5%)	0.02
Triglycerides >REF, n	12 (38.8%)	36 (33.3 %)	0.58
Glucose >REF, n	5 (16.1%)	11 (10.2%)	0.36

REF, reference value, AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatases; REF, reference value.

Table 4. Risk factors of transaminase increase

		Agomelatine 25-50mg			Placebo		
Model		Effective by classes	Event by classes	HR [95CI%]	Effective by classes	Event by classes	HR [95CI%]
Age (years)	>65 vs ≤65	557 vs 7048	10 vs 121	1.04[0.54;1.98]	263 vs 1366	2 vs 6	1.72[0.35;8.59]
Gender	Female vs Male	5230 vs 2375	85 vs 46	0.83[0.58;1.18]	1113 vs 516	7 vs 1	3.34[0.41;27.25]
Baseline AST	>REF vs ≤REF	260 vs 7345	13 vs 118	3.41[1.92;6.04]**	73 vs 1556	1 vs 7	3.59[0.44;29.27]
Baseline ALT	>REF vs ≤REF	590 vs 7015	20 vs 111	2.29[1.42;3.69]**	136 vs 1493	4 vs 4	10.69[2.67;42.75]**
Baseline ALT or AST	>REF vs ≤REF	675 vs 6930	23 vs 108	2.35[1.50;3.69]**	157 vs 1472	4 vs 4	9.35[2.34;37.42]*
Baseline GGT	>REF vs ≤REF	735 vs 6870	33 vs 98	3.23[2.18;4.79]**	185 vs 1444	4 vs 4	8.14[2.04;32.56]*
Baseline Triglycerides	>REF vs ≤REF	1969 vs 5589	45 vs 84	1.49[1.03;2.13]*	404 vs 1206	3 vs 5	1.79[0.43;7.52]
Baseline ALP	>REF vs ≤REF	217 vs 7388	5 vs 126	1.35[0.55;3.29]	45 vs 1584	1 vs 7	5.74[0.70;47.04]
Metabolic syndrome	Yes vs No	1112 vs 6493	36 vs 95	2.08[1.42;3.06]**	242 vs 1387	1 vs 7	0.78[0.10;6.31]
- BMI (kg/m²)	≥30 vs <30	1716 vs 5858	45 vs 86	1.67[1.17;2.40]*	318 vs 1304	1 vs 7	0.56[0.07;4.55]
-Elevated Triglyceride	Yes vs No	2501 vs 5104	53 vs 78	1.35[0.95;1.92]	517 vs 1112	3 vs 5	1.30[0.31;5.45]
-Elevated Cholesterol	Yes vs No	759 vs 6846	24 vs 107	1.89[1.21;2.94]*	163 vs 1466	8 vs 0	NA
-Elevated blood pressure	Yes vs No	3370 vs 4235	70 vs 61	1.39[0.98;1.96]	830 vs 799	4 vs 4	0.90 [0.22;3.59]
- Elevated blood glucose	Yes vs No	842 vs 6763	17 vs 114	1.18[0.71;1.97]	197 vs 1432	1 vs 7	0.95 [0.12;7.74]

** <0.001 ; * <0.05

Metabolic syndrome is defined by the presence of at least 3 of the following factors: BMI ≥ 30 kg/m², elevated triglycerides (medical history or ≥ 1.6mmol/L), elevated cholesterol (medical history or ≥ 8 mmol/L), elevated blood pressure (medical history, SBP≥130 mmHg or DBP ≥ 85 mmHg), elevated blood glucose (medical history or ≥6.1 mmol/L). AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatases; REF, reference value.

Table 5. Transaminase elevation according to baseline level of transaminase

	Agomelatine		Placebo		Cox proportional hazard models		Interaction
	N	n(%)	N	n(%)	Hazard Ratio [95%CI]	P-value	P-value
AST or ALT > 3 ULN							
Baseline ≤ REF	6930	108(1.56)	1472	4(0.27)	4.10 [1.51;11.13]	0.006	
Baseline > REF	674	23(3.41)	157	4(2.55)	0.98 [0.34; 2.85]	0.973	0.0556
AST or ALT > 5 ULN							
Baseline ≤ REF	6930	54(0.78)	1472	3(0.20)	2.61 [0.81; 8.36]	0.107	
Baseline > REF	674	9(1.34)	157	2(1.27)	0.73 [0.16; 3.39]	0.686	0.2032
AST or ALT > 10 ULN							
Baseline ≤ REF	6930	19(0.27)	1472	1(0.07)			
Baseline > REF	674	1(0.15)	157	0(0.00)			

Hazard Ratio were not provided for AST or ALT >10 ULN due to the small number of cases.
REF, reference value.

8. FIGURE LEGENDS

Figure 1

Flow chart. Inclusion of patients and analyses by the Liver Safety Committee.

Figure 2

Time to onset of transaminase increase in cases classified as probably or possibly related to agomelatine. **A**. In all patients possibly/probably related (N=86). **B**. In patients with adaptive phenomenon (N=31).

Compliance with ethical standards

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