1. ABSTRACT

Title

Post-Authorisation Safety Study of Agomelatine and the Risk of Hospitalisation for Acute Liver Injury

Keywords

Acute liver injury; agomelatine; risk; antidepressants

Rationale and Background

Agomelatine (Valdoxan, Thymanax) is a melatonergic agonist and 5-HT2C antagonist indicated for major depressive episodes in adults. Hepatotoxic reactions are an identified risk of agomelatine included in the European risk management plan. The goal of this post-authorisation safety study (PASS) is to evaluate the risk of acute liver injury (ALI) associated with agomelatine as used in current medical practice in comparison with other antidepressant drugs.

Research Question and Objectives

The primary objective of the study was to estimate, with the nested case-control analysis, the fully adjusted odds ratio (OR) of hospitalisation for ALI comparing new users of agomelatine and other antidepressants with new users of citalopram.

The secondary objective of the study was to estimate the age- and sex-standardised incidence rates of hospitalisation for ALI among new users of antidepressants and the age- and sex-adjusted incidence rate ratios by comparison with citalopram.

Study Design and Study Period

This is a large, multinational, retrospective longitudinal cohort and nested case-control study of new users of agomelatine (main exposure of interest), and of eight other study antidepressants new users compared with new users of citalopram (common reference group). The study period in each data source started after agomelatine launch in each country (in 2009 or 2010) and ended with the last year for which data were available in each data source (2013 or 2014).

Setting

The source population included all individuals aged 18 years or older at the date of the first-recorded prescription fill of any of the study antidepressants on the study period(s).

This study was conducted in automated health databases in four countries: Spain (SIDIAP [Information System for Research in Primary Care] and EpiChron Cohort [EpiChron Research Group on Chronic Diseases]), Germany (GePaRD [German Pharmacoepidemiological Research Database]), and the national registers in Denmark and Sweden. An external validation study was conducted in the Oldenburg hospital, Germany.

Subjects and Study Size, Including Dropouts

The study cohort included adults with at least 12 months of continuous enrolment in the data source with a first-recorded prescription fill of one of the study antidepressants during the study period and had not received a prescription fill for the same study antidepressant within the prior 12 months (new users). For women, an additional eligibility criterion was absence of pregnancy at the start date. Patients with a history of liver disease or risk factors for liver disease, chronic biliary or pancreatic disease, malignancy, or other life-threatening conditions were excluded from the study cohort.

All cases identified in the study cohort were included in the nested case-control study. Controls were selected from the study cohort using density sampling. Up to 20 controls per case were randomly selected from the risk set of each case. Controls were matched to cases on index date, age, calendar year of start date (the year of entry in the cohort), and sex. The same year of birth was used to match by age.

The study size was driven by the uptake of agomelatine and was estimated in the protocol to range from 65,000 to 92,000 agomelatine users. With this study size, and based on the incidence of hospitalisation for ALI found in the literature, the minimum OR to be detected in the nested case-control study with an 80% power ranges from 2.1 to 6.8 for the scenario with the lowest number of users of agomelatine and from 1.9 to 5.6 for the scenario with the highest number of users of agomelatine. The final number of agomelatine new users included in the study across all data sources was 74,400 in the main analysis and 117,240 in the sensitivity analysis without exclusion criteria.

Variables and Data Sources

The primary endpoint was ascertained in all data sources and was defined as any patient with a specific hospital discharge diagnosis code (ICD-9/ICD-10[*]) for ALI.

The secondary endpoint was defined by specific and non-specific hospital discharge diagnosis codes and was evaluated only in Spain and Denmark in which validation of this less specific outcome was implemented.

The exploratory tertiary endpoint was assessed using specific and non-specific codes identified in both hospital and ambulatory settings, and the endpoint was evaluated in all data sources whether or not validation was feasible. A sensitivity analysis restricted to validated cases was planned in the three data sources where validation was implemented.

In Germany, an external validation study (ALIVAL) of the ICD discharge diagnosis codes for ALI (primary and tertiary endpoints) reported in a German hospital was set up to estimate the positive predictive value (PPV) of algorithms used in the GePaRD.

Confounding factors were those related to the risk of ALI and to exposure to agomelatine or to another study antidepressant. Age and sex were included as potential risk factors in both the cohort and nested case-control analyses, while alcohol use, obesity, other components of metabolic syndrome (hypertension and dyslipidaemia), diabetes, inflammatory bowel disease,

[*] ICD-9-CM = *International Classification of Diseases, 9th Revision*; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

preexisting chronic liver diseases, acute biliary and pancreatic disease, peptic ulcer disease, and rheumatic diseases were included only in the nested case-control analysis.

Crude and adjusted ORs and 95% confidence intervals (CIs) for ALI were estimated using conditional logistic regression models. Using citalopram current use as the reference category, crude and adjusted ORs for ALI were estimated for current use of each study antidepressant. To check the robustness of the results, several sensitivity analyses were performed. Two post hoc sensitivity analyses were implemented (recommended by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency [PRAC] in the assessment of the study interim report). In one, no exclusion criteria were implemented, and in the other all study exclusion criteria were applied except the ones related to alcohol used disorder and drug abuse.

Results

A total of 3,238,495 new users of antidepressants (EpiChron, n = 185,628; SIDIAP, n = 203,101; the GePaRD, n = 817,072; the Danish National Health Registers, n = 664,205; and the Swedish National Registers in Sweden, n = 1,368,489) were included in the main analysis, of which 74,440 were new users of agomelatine. The first sensitivity analysis requested by the PRAC without any exclusion criteria included 4,833,774 new users of antidepressants, of which 117,240 were new users of agomelatine. The second sensitivity analysis requested by the PRAC with exclusion criteria applied except alcohol and drug abuse included 3,531,529 new users of antidepressants, of which 84,210 were new users of agomelatine.

Results of the direct validation performed in EpiChron, SIDIAP, and the Danish National Health Registers are presented in Table (1) 1. In addition, results from the ALIVAL external validation study are also presented in the same table.

Table (1) 1 - Positive predictive values of the different study endpoints estimated in the direct validation implemented in Spain and Denmark and the external validation study implemented in Germany (ALIVAL)

	Direct Validation			External Validation
	EpiChron PPV (95% CI)	**SIDIAP PPV (95% CI)**	**Danish National Health Registers PPV (95% CI)**	**ALIVAL PPV (95% CI)**
Primary endpoint (specific codes, hospitalised patients)	84.2 (60.4 - 96.6)	60.0 (26.2 - 87.8)	74.0 (59.7 - 85.4)	62.7 (50.0 - 74.2)
Secondary endpoint (specific and non-specific codes, hospitalised patients)	64.5 (45.4 - 80.8)	40.0 (19.1 - 63.9)	70.4 (63.8 - 76.5)	NA
Tertiary endpoint (specific and non-specific codes, hospitalised and ambulatory patients)	25.4 (18.3 - 33.6)	7.7 (6.6 - 8.9)	47.0 (42.2 - 51.7)	45.1[a] (36.7 - 53.6)

CI = confidence interval; NA = not available; PPV = positive predictive value (percentage).
[a] *Restricted to patients hospitalised or seen at hospital clinics. In the GePaRD, patients from hospital and non-hospital settings were included and therefore this PPV is not directly applicable to the GePaRD.*

Primary study endpoint

A total of 472 cases of ALI hospitalisation were identified, ranging from 19 (SIDIAP) to 170 (Danish National Health Registers). The specific codes used to identify cases of the primary endpoint had a high positive predictive value. The PPVs ranged from 60% (SIDIAP) to 84% (EpiChron) in the study data sources and was 62.7% in the external validation study in Germany (ALIVAL).

Results of the case-control analyses for the current use of agomelatine compared with current use of citalopram for the primary endpoint are presented in Table (1) 2.

Table (1) 2 - Results for the primary endpoint and current use (agomelatine *vs.* citalopram) in each data source and combined in the main analysis and the two sensitivity analyses recommended by the PRAC

	EpiChron OR (95% CI)	SIDIAP OR (95% CI)	GePaRD OR (95% CI)	Danish National Health Registers OR (95% CI)	Swedish National Registers OR (95% CI)	Combined OR (95% CI)
Main analysis	**0.82 (0.06 - 10.70)**	-	**0.55 (0.06 - 4.72)**	**0.30 (0.04 - 2.32)**	-	**0.48 (0.13 - 1.71)**
Sensitivity analyses						
PRAC-1 No exclusion criteria applied	0.66 (0.06 - 7.16)	0.61 (0.08 - 4.87)	0.36 (0.10 - 1.39)	0.32 (0.12 - 0.84)	0.26 (0.01 - 8.17)	0.37 (0.19 - 0.74)
PRAC-2 Exclusion criteria except alcohol and drug abuse applied	1.60 (0.12 - 21.33)	1.43 (0.15 - 13.84)	0.51 (0.08 - 3.03)	0.30 (0.09 - 1.00)	0.16 (0.01 - 3.85)	0.47 (0.20 - 1.07)

"-" indicates that the model did not converge. ALI = acute liver injury; CI = confidence interval; OR = odds ratio; PRAC = Pharmacovigilance Risk Assessment Committee (of the European Medicines Agency).
Note: Adjusted for confounding factors; the list of confounders differed by data source.

Results of the planned sensitivity analyses were consistent with the main analysis and produced combined OR estimates for agomelatine below 1.00 for current use.

Secondary study endpoint

This endpoint included only cases that had been confirmed after validation, which resulted in a lower number of events than for the primary endpoint. A total of 178 confirmed cases and 3,540 controls were identified. Most of the cases were identified in Denmark (150); 20 cases were identified in EpiChron and 8 in SIDIAP.

Confirmed cases during current use of agomelatine were identified in Denmark only, the adjusted OR estimate for current use was 0.40 (95% CI, 0.05 - 3.02).

Tertiary study endpoint

Overall, there were 17,118 cases of the tertiary study endpoint and 342,070 controls.). The GePaRD had overall the largest number of cases (11,917), followed by SIDIAP (2,826), Sweden (1,099), Denmark (1,088), and EpiChron (268). In Sweden, no validation of cases was implemented.

The PPV of the algorithm to identify tertiary endpoint cases was low in all data sources but especially in SIDIAP (7.7%). The highest PPV (47.0%) were found in Denmark and in the ALIVAL external study (Germany, 45.1%). The PPV in ALIVAL was based on hospital inpatient and outpatient cases only and cannot be directly applied to all cases identified in the GePaRD (see Section 11.2.1). In EpiChron, the PPV was 25.4%. In Sweden, no validation of cases was implemented.

The results for current use of agomelatine were different in the GePaRD, where adjusted OR estimates were precise and above 1.00 (1.24; 95% CI, 1.07 - 1.42), when compared with the other four data sources, especially those in Denmark and Sweden, where OR estimates were about 0.5. In Denmark, the adjusted OR estimate for current use of agomelatine was 0.44 (95% CI, 0.22 - 0.87).

The combined estimate for agomelatine for current use was 0.79 (95% CI, 0.50 - 1.25). The results were heterogeneous.

The planned sensitivity analyses that included only idiopathic cases could be only conducted in Denmark and produced estimates for agomelatine that were also below 1.00. The OR for current use was 0.90 (95% CI, 0.21 - 3.93).

Discussion

Limitations

As in any study in automated data we rely on the completeness and accuracy of the recorded information, which may impact the validity of the data regarding exposure status, occurrence of incident events, and ascertainment of the covariates to be included in the multivariable models. In this study, this is likely to have resulted in non-differential misclassification of the endpoints, potentially biasing the estimates towards unity.

Ascertainment of incident events and potential confounding variables included in the regression models was based on diagnostic codes. Misclassification was also possible. To minimise misclassification of endpoints, specific codes were used for the primary endpoint and validation of the secondary endpoint was implemented.

The sources of information differed across data sources, which may explain some of the differences observed in the prevalence of some clinical features, as well as the differences observed in some OR estimates across the study data sources.

All data sources had a limited number of identified events of the primary endpoint. For agomelatine, OR estimates for current use were based on only one case in EpiChron and the GePaRD and on fewer than five cases in Denmark; no cases were identified in SIDIAP or Sweden. The number of ALI cases for the primary endpoint in the other study antidepressant cohorts was also low in the five data sources, often yielding estimates with either zero cases or wide CIs. For the secondary endpoint, the study size limitations were greater than for the primary endpoint because only confirmed cases from three data sources were included. For the tertiary endpoint, the number of cases was much higher (especially in the GePaRD and SIDIAP), yet the low PPVs observed for this endpoint definition limit the interpretation of these results.

Finally, the limited number of identified ALI cases for the primary and secondary endpoints also impacted the multivariable logistic regression strategy. To ensure a sufficient case-to-covariate ratio, the number of covariates and the number of categories for categorical covariates included in the models had to be minimised. This resulted in more statistically stable models, but it may have increased the risk of residual confounding. Nevertheless, the restrictive inclusion criteria implemented likely excluded most of the key potential confounders associated with ALI. On the other hand, the post hoc analysis that did not impose any exclusion criteria resulted in a much larger number of new users of agomelatine (117,240) and of other antidepressants (4.8 million overall) and yielded more precise OR estimates for the primary endpoint that were consistent with the ones obtained in the main analysis.

Interpretation

The study had important strengths, and the study team implemented all possible measures, including studying information never used before in many of the data sources, to address the above limitations, some of which are shared by all studies conducted with secondary data collection. Of the key strengths, first, it is the largest study conducted to date in routine clinical care conditions evaluating the risk of ALI in the largest number of antidepressants studied at one time, and the study included important endpoint validation efforts. Second, inclusion of multiple independent data sources and populations from different countries allowed evaluation of the consistency of the findings across five different, heterogeneous automated health care data sources. Third, including three different endpoints with various degrees of positive predictive value and yielding a varying number of potential cases created different perspectives for interpreting the study results. Finally, the validation activities implemented provided PPV estimates that facilitate the interpretation of the study results.

The analysis of the primary endpoint combined an endpoint with high positive predictive value and a large study size, while at the same time controlling for confounding as much as the data allowed. The results did not suggest that agomelatine use increases the risk of

hospitalisation for ALI when compared with citalopram. The single and combined OR point estimates were imprecise in the main analyses, but the sensitivity analysis without exclusion criteria (with better precision) and the many other sensitivity analyse conducted further supports that there is no increase in risk of hospitalisation for ALI for current use of agomelatine. These results do not suggest a public health problem, at least among patient populations in health care systems with similar prescription patterns and risk minimisation measures to those in this study.

The primary endpoint was also studied in a population that included patients with alcohol and drug abuse related conditions in contrast with the main analysis in which those patients were excluded. No increase risk (adjusted combined OR for current use 0.47; 95% CI, 0.20 - 1.07) was observed in that population. However, individual data source results were heterogeneous. Both EpiChron and SIDIAP that had the smallest agomelatine cohorts showed OR estimates above 1.00 with wide 95% CI. Similarly, no increase risk (adjusted OR for current use, 0.37; 95% CI, 0.19 - 0.74) was observed in the largest population of new users with no exclusions that included patients with liver conditions that increased their risk of ALI and the risk estimates were more precise.

Results for the secondary endpoint had the highest validity because the endpoint included only confirmed cases. As for the other endpoints, there was no evidence of an increased risk of hospitalisation for ALI associated with the use of agomelatine. Estimates were less precise because they could be calculated only in Denmark.

With regards to the tertiary endpoint, the low PPV of the tertiary endpoint (7.7% in SIDIAP, 25.4% in EpiChron, and 47.0% in Denmark) should be considered when interpreting results from analyses of the tertiary endpoint. In addition, in the GePaRD, outpatient codes are dated only quarterly, are of different degrees of diagnostic certainty, and direct validation was not possible. Moreover, given the similar and large proportion of tertiary endpoint cases in relation to the size of the cohorts in SIDIAP and the GePaRD and the low PPV in SIDIAP (7.7%), the PPV in the GePaRD for this endpoint was expected to be low. The PPVs obtained from the ALIVAL study can be applied to the primary endpoint in the GePaRD, but, as mentioned previously, cannot be directly applied to the tertiary endpoint.

The sensitivity analysis including only validated cases of the tertiary endpoint in Denmark provided a more valid OR point estimate for current use of agomelatine than the one from the tertiary endpoint main analysis but with less precision. The direction of this point estimate (OR, 0.75; 95% CI, 0.17 - 3.22) is consistent with the estimates obtained for the primary endpoint in Denmark in both the main and the sensitivity analyses

Patients taking agomelatine undergo routine liver enzyme monitoring. Therefore, liver enzyme elevations may be more likely to be detected in this group and prevent patients from starting treatment with agomelatine; or, if treatment has been started, treatment may be stopped earlier or cases of liver injury are detected earlier than if liver enzyme monitoring had not been conducted. In the context of observational studies using data from routine clinical practice, this could lead to selective prescribing, to surveillance bias or both. Thus, the monitoring could bias the results, potentially in opposite directions. Surveillance bias is unlikely to have had a large impact on the reported estimates for the primary and secondary endpoints that included only hospitalised cases. In the combined results, no risk increase was found for the tertiary endpoint, which was in principle more sensitive to surveillance bias and misclassification than the primary and secondary endpoints. Surveillance bias would have

resulted in risk estimates above 1.00. On the other hand, in the context of low PPVs, non-differential misclassification would produce bias towards the null.

In some data sources where the number of cases of the primary and secondary endpoints was very small, adjustment for potential confounders was limited. Thus, the possibility of residual confounding cannot be discarded. However, similar results were observed in the largest population without exclusion criteria and control of confounding via multivariable models did not have the limitations encountered in the main analysis of the primary endpoint.

In this study, analyses of most study antidepressants yielded odds ratios of ALI hospitalisation lower than 1.00 when compared with citalopram in the combined analyses for the primary and secondary endpoints. The consistency in the direction of this association across antidepressants was unexpected. However, the limitations discussed previously, particularly those related to the low number of cases, preclude drawing definite conclusions. Citalopram is in many countries one of the first-line treatment options, which could potentially result into confounding by indication, but other antidepressants in this study share a similar drug prescription pattern. On the other hand, results from two more recent studies indicate that citalopram may increase the risk of ALI. Both studies had low precision in their risk estimates and the studies were not specifically designed to estimate the risk of ALI associated with citalopram use.

The estimates of risk associated with agomelatine use in this study are consistent with those from a recent cohort study funded by the French National Agency for Medicines and Health Products Safety and conducted using the French Health Insurance database. This study did not find any increased risk of severe liver injury associated with the use of agomelatine compared with use of selective serotonin reuptake inhibitors (adjusted hazard ratio, 1.07; 95% CI, 0.51 - 2.23).

Conclusion

Use of agomelatine was not associated with higher risk of ALI hospitalisation compared with use of citalopram in a large cohort comprising 3.2 million new users of antidepressants, of which 74,440 were agomelatine new users (in an unrestricted population sensitivity analysis, 4.8 million overall and 117,240 agomelatine new users), in five populations in Spain, Denmark, Sweden, and Germany. Precision of the combined risk estimates was low for the primary endpoint but the results were similar and more precise in the unrestricted sensitivity analyses and consistent with other analyses and for other endpoints. In the combined analysis, no increase in risk was observed in populations including alcoholic patients or with other various risk factors. These results do not suggest that risk of ALI with use of agomelatine constitutes a public health problem, at least among patient populations in health care systems with prescription patterns and risk minimisation measures similar to those in this study.

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