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Effects of adjunctive eslicarbazepine acetate on serum lipids in patients with partial-onset seizures: Impact of concomitant statins and enzyme-inducing antiepileptic drugs.

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Effects of adjunctive eslicarbazepine acetate on serum lipids in patients with partial-onset seizures: Impact of concomitant statins and enzyme-inducing antiepileptic drugs

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Keywords: Eslicarbazepine acetate, Statins, Serum lipids, Partial-onset seizures, Adjunctive, Enzyme-inducing antiepileptic drugs

ABSTRACT

Purpose: To evaluate the effects of eslicarbazepine acetate (ESL) on lipid metabolism and to determine whether reduced statin exposure during ESL therapy has clinical consequences.

Subjects and methods: We conducted a post-hoc analysis of pooled data for serum lipids (laboratory values) from three phase III, multicenter, randomized, double-blind, placebo-controlled trials of adjunctive ESL therapy (400, 800, or 1200 mg once daily) in patients with treatment-refractory partial-onset seizures. Changes from baseline in serum lipid levels were analyzed according to use of statins and/or enzyme-inducing antiepileptic drugs (EIAEDs) during the baseline period.

Key findings: In total, 426 and 1021 placebo- and ESL-treated patients, respectively, were included in the analysis. With regard to the changes from baseline in serum concentrations, there were statistically significant differences between the placebo and ESL 1200 mg QD groups, for both total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C), but the effect sizes were small (+4.1 mg/dL and +1.8 mg/dL, respectively). A small but significant difference in low-density lipoprotein cholesterol (LDL-C; −5.0 mg/dL) was observed between the ESL 400 mg QD group and the placebo group. In patients not taking a concomitant EIAED, there were no changes with ESL 400 mg QD, but modest and statistically significant increases in cholesterol fractions (TC, LDL-C and HDL-C) with ESL 800 mg QD (−6 mg/dL) and ESL 1200 mg QD (−10 mg/dL). ESL had no consistent effects on serum lipids, although the subgroups were small.

Significance: These results suggest that ESL does not appear to have clinically significant effects on serum lipids, nor does the pharmacokinetic interaction between ESL and statins have an impact on serum lipid concentrations.

1. Introduction

Mounting evidence has linked the use of enzyme-inducing antiepileptic drugs (EIAEDs), particularly carbamazepine and phenytoin, with elevations in serum lipids (Brämswig et al., 2003; Chuang et al., 2012; Mintzer et al., 2009; LoPinto-Khoury and Mintzer, 2010).
These drugs appear to have inherent lipid-elevating properties, likely due to induction of the CYP450 enzymes of the cholesterol synthesis pathway (Gibbons, 2002; Mintzer and Mattson, 2009).

In patients receiving treatment for hypercholesterolemia, there is concern that AEDs may exacerbate their condition by inducing metabolism of HMG-CoA reductase inhibitors (‘statins’). Statins are the most commonly used lipid-lowering agents, and most are broken down by hepatic enzymes. Carbamazepine has been specifically shown to reduce the area under the curve for simvastatin concentrations by 75% (Ucar et al., 2004), while phenytoin has demonstrated a similar interaction with atorvastatin (Bullman et al., 2011). It is possible that other effects of AEDs may contribute to the reduced bioavailability of statins reported during concomitant administration (Gidal et al., 2017). However, none of these studies evaluated the effect of AEDs on serum lipid levels.

The antiepileptic drug (AED) eslicarbazepine acetate (ESL), approved in the U.S. and Europe as once-daily treatment for focal seizures, underwent several Phase II and Phase III trials in both epilepsy and non-epilepsy populations on the road to regulatory approval. As part of the safety evaluation, these trials included monitoring of a number of serologic parameters, including serum lipids. Some of the patients in these trials were being treated concomitantly with statins; this is relevant because use of ESL has been shown to lead to significant reductions in plasma exposure to both simvastatin (Bialer and Soares-da-Silva, 2012; Falcão et al., 2013) and rosuvastatin (Gidal et al., 2017). As and its active entity are CYP3A4 substrates, this interaction is most likely due to CYP3A4 induction by ESL (Bialer and Soares-da-Silva, 2012; Falcão et al., 2013). The latter interaction is more curious, as rosuvastatin undergoes minimal enzymatic metabolism, and the nature of the ESL-rosuvastatin interaction is not well understood at present (Gidal et al., 2017). Moreover, the clinical impact of reduced statin exposure, while assumed, has never been directly demonstrated in any study of any AED.

Here we report aggregated lipid data from clinical trials of ESL in patients with epilepsy. Our investigation had two goals: first to ascertain whether ESL has any direct effect on lipid metabolism; and second to determine whether reduced statin exposure during ESL therapy has clinical consequences, by measuring the endpoint of statin treatment — serum lipid levels — in statin users taking ESL.

2. Methods

2.1. Studies

This is a post-hoc analysis of pooled lipid data from three Phase III epilepsy trials (2093-301, 2093-302 and 2093-304 [ClinicalTrials.gov identifiers: NCT00957684, NCT00957684 and NCT00988429, respectively]. Each was a multicenter, randomized, double-blind, placebo-controlled study in patients with treatment-refractory partial-onset seizures. Individual details of each trial have been reported (Ben-Menachem et al., 2010; Elger et al., 2009; Sperling et al., 2015); briefly, the pooled population from these clinical trials comprised patients aged 16 or older, taking between 1 and 3 concomitant AEDs. All trials had, as part of the protocol, the requirement that concomitant AEDs be maintained at stable doses throughout the double-blind portion of the trial. Each study had an 8-week baseline period, followed by a 2-week double-blind titration period and a 12-week double-blind, fixed-dose maintenance period. At the end of the baseline period, patients were randomized to one of 3 or 4 treatment arms (placebo and ESL doses of 400, 800, or 1200 mg QD, depending on the study).

A fourth multicenter, randomized, double-blind, placebo-controlled phase III study (2093-303 [NCT00957372]) has also been conducted. The findings of this study (Gil-Nagel et al., 2009) were consistent with those of studies −301, −302 and −304, but the study was deemed not to be in full accordance with Good Clinical Practice (GCP) standards. Consequently, in the analysis of safety and effectiveness of ESL conducted as part of the New Drug Application submitted to the Food and Drug Administration for ESL, data from study −303 were not considered by the regulator, nor have they been included in this analysis.

2.2. Serum lipid measurements and data analysis

In all trials, blood samples were taken for assessment of standard blood chemistry, hematology and coagulation parameters. Data were analyzed according to whether or not patients were taking statins and/or ESL during the 8-week baseline period. For the purpose of the analysis, baseline statin use was used as an indicator of concomitant use, on the assumption that changes in statin use were unlikely to have occurred during the relatively brief duration of the trials. As use of AEDs during baseline was specified to continue throughout the trials, baseline ESL use should be equivalent to concomitant use. The means and standard deviations of the changes in serum lipid levels from baseline to the final visit (end of study, or early termination visit) were calculated. Baseline was defined as the last visit prior to the first dose of study medication. Lipid measurements included total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TRIG). Non-fasting measurements were obtained, as recommended by the Joint Consensus Initiative of the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine (Nordestgaard et al., 2016). A generalized linear model was used to determine the overall effect of treatment on changes from baseline in serum lipid concentrations (effect size: each ESL dose group versus placebo). A separate generalized linear model was used to evaluate the effect of treatment in patients taking or not taking ESL during the baseline period and a third model was used to assess effect size in patients taking or not taking an ESL during or after the baseline period.

ESL used by one or more patients during the baseline period included carbamazepine, phenytoin, and phenobarbital. The statins used by patients during the trial included simvastatin, atorvastatin, pravastatin, rosuvastatin, lovastatin and fluvastatin.

Data are presented for the safety population (all patients who received at least one dose of study medication).

3. Results

3.1. Baseline characteristics and exposure to ESL

The safety population comprised 426 and 1021 placebo- and ESL-treated patients, respectively (Table 1). The mean daily dose for ESL-treated patients was 785 mg, and the median duration of ESL exposure was 98 days.

Patient demographics were well balanced across the treatment groups, with approximately equal numbers of males and females, and mean age approximately 38 years in all groups (median 37–38 years; Table 1). The majority of patients (97% of both the placebo and total ESL groups) were taking 1–2 AEDs during the baseline period; the most commonly used AEDs during baseline were carbamazepine, lamotrigine, valproic acid, and levetiracetam. Approximately 60% of patients were receiving an ESL during the baseline period (placebo group, 60%; ESL groups, 61%). During the baseline, statins were used by 18 patients taking placebo (4%) and 46 taking ESL (5%); statin use is shown in Table 2; some patients received > 1 drug.

3.2. Serum lipid concentrations

Fig. 1 shows mean changes in lipid levels from baseline to end of study/early-termination visit, in patients who were taking or were not taking statins during baseline. Effect sizes (differences in the change from baseline in serum lipid concentrations between the treatment groups and the placebo group) and related levels of statistical
The effect of ESL on serum lipids in the overall population is shown in Fig. 2. As can be seen, differences in the change from baseline in serum lipid concentration between the placebo group and the ESL groups were very modest (< 10 mg/dL); the differences were non-significant at ESL 800 mg QD and significant for TC and HDL-C at 1200 mg QD, but the magnitude of effect was very small (approximately 4 mg/dL and 2 mg/dL, respectively). At 400 mg QD, the difference in LDL-C was significant, but again the effect size was small (≤ 5 mg/dL).

3.4. Impact of EIAED use

Since it is known that EIAEDs have a substantial effect on serum lipids, we evaluated changes from baseline in serum lipid concentrations during ESL therapy (separately for patients who were and were not taking EIAEDs). Fig. 3 summarizes the changes from baseline in serum lipid concentrations (effect size versus placebo) during ESL therapy, according to use of EIAEDs. In ESL-treated patients who were not taking an EIAED during the baseline period, there was an apparent effect of ESL on cholesterol fractions (TC, LDL-C and HDL-C); for TC and HDL-C, the effect appeared to be dose-related. No effects were apparent in the ESL 400 mg QD dose group; significant elevations in TC and LDL-C (relative to placebo) occurred in the ESL 800 mg QD dose group, and larger elevations in TC and HDL-C were seen in the ESL 1200 mg QD dose group, along with a similarly-sized elevation for LDL-C, with the differences being significant for all three measures. The effect sizes were quite modest even at the highest dose (3–5 mg/dL for the
cholesterol fractions, 9 mg/dL for TC). TRIG was not significantly affected by ESL at any dose. In patients who were taking an EIAED, no consistent effect of ESL on lipids was apparent.

3.5. Statin-treated patients

Finally, we examined the impact of ESL on lipids in patients who were being treated with a statin. Again, the data are summarized according to use of EIAEDs, as this class of drugs is known to have substantial pharmacokinetic interactions with at least some statins, and this could confound the impact of ESL on the effects of the statins. Fig. 4 summarizes the effect sizes for change from baseline in serum lipid concentrations, according to use of EIAEDs and statins. Note that data for the ESL 400 mg QD group are not reported for patients taking or not taking an EIAED during baseline, as only one patient in each subgroup who received this dose were taking a statin. Among statin users who were not taking an EIAED, there was no significant effect of ESL on serum lipids (Fig. 4A, left panel). In a similarly-sized group who took both an EIAED and a statin (ESL 400 mg, n = 1; ESL 800 mg, n = 9; ESL 1200 mg, n = 10; placebo: n = 10) (Fig. 4B, left panel). Among patients who were taking neither a statin nor an EIAED, there was a modest increase in TC, LDL-C...
and HDL-C in the ESL 1200 mg group (Fig. 4A, right panel), similar to the effect described in the preceding paragraph (among patients who were not taking an EIAED, but may or may not have been taking a statin).

4. Discussion

Our examination of the effect of ESL on lipids in epilepsy patients yielded 3 main findings. First, ESL had no effect on serum lipid concentrations in patients who were being treated with concomitant EIAEDs. This makes sense insofar as AED-induced lipid alterations are believed to be due to effects on CYP450 enzymes (Mintzer and Mattson, 2009), and ESL may be a less potent inducer of CYP450 enzymes than drugs such as carbamazepine and phenytoin. This would imply that in patients taking an EIAED, many such enzymes are in an “induced” state, so adding ESL does not lead to any further enzyme induction.

To evaluate any direct effects of ESL on lipid levels, it is necessary to investigate patients who are not being treated with an EIAED. The results in this subgroup yield our second finding, which is that ESL has only a very modest effect on serum lipids. In contrast to carbamazepine, which appears to increase TC by approximately 25 mg/dL, regardless of dose (Mintzer et al., 2009), the effect of ESL on TC was dose-dependent; even the highest dose led to an increase of only 9 mg/dL. The difference was statistically significant, suggesting that it may have been a drug effect, although the post-hoc nature of the analysis and the fact that there was no adjustment for multiplicity means that all conclusions must be tempered with caution; the magnitude of the difference, however, was well below the threshold that most clinicians would consider to be clinically significant, and in the moderate-dose group the difference was smaller still. This suggests that ESL may not be associated with clinically meaningful hyperlipidemia.

Third, and most intriguing, are the findings in statin-treated patients. Like carbamazepine (Ucar et al., 2004), ESL has also been shown to substantially reduce exposure to simvastatin, presumably by inducing the metabolizing enzymes (Falcão et al., 2013). It would be expected that other statins metabolized by the CYP450 system (such as

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Fig. 4. Effect of ESL on changes from baseline in serum lipid levels according to concomitant (baseline) use of EIAEDs and statins. (A) Patients not taking an EIAED during baseline. (B) Patients taking an EIAED during baseline.

The data are effect sizes (ESL minus placebo) for the change in serum lipid concentration between baseline and end of study/early-termination visit. *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 versus placebo (Wald test).

\*n = 150; \*n = 154; \*n = 222; \*n = 223.

ESL, eslicarbazepine acetate; EIAEDs, enzyme-inducing antiepileptic drugs; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TRIG, triglycerides.
lovasatin and atorvastatin) should be similarly affected. In turn, it would be expected that the marked reductions in statin exposure engendered by the AEDs would lead to reductions in the efficacy of the statins, resulting in elevations in serum cholesterol. Yet the current data show that use of ESL in patients taking statins did not lead to meaningful changes in serum lipid concentrations. This suggests that standard drug interaction studies, which evaluate statin exposure by measuring AUC and pharmacodynamic parameters (other than lipid concentrations) may not truly reflect the clinical function of the drug in this context. The reasons for this are unclear, although the evidence for a pharmacokinetic interaction between ESL and the statins was derived from studies conducted in relatively small numbers of healthy volunteers (less than 30) who took ESL followed by a single dose of the different statins (Bialer and Soares-da-Silva, 2012; Gidal et al., 2017). The scenarios examined by the current analyses reflect chronic dosing, and therefore resemble more closely the concomitant use of these medications in day-to-day clinical practice, which may be more informative for clinicians. Another potential explanation could be that ESL might reduce plasma exposure to some statins, not by inducing their hepatic metabolism, but by increasing their uptake from the plasma compartment into hepatocytes by membrane transporters (Gidal et al., 2017). Since hepatocytes are the ultimate site of action of statins in reducing plasma lipid levels, this speculative interaction may not lead to alterations in cholesterol-lowering function, even with an apparent reduction in plasma statin levels. However, the exact effect of eslicarbazepine on these transporters is not currently understood, and further research will be required to determine the underlying mechanisms. Future work is likewise needed to ascertain whether pharmacokinetic interactions between carbamazepine and statins, and between phenytoin and statins, are functionally meaningful.

The effect of ESL on serum lipids appears similar to that of the related drug oxcarbazepine, which also produces modest, clinically-insignificant increases in serum lipids (Garoufi et al., 2014; Kim et al., 2013). As mentioned previously, the original compound in the class, carbamazepine, causes substantial elevations in serum lipids, lipoprotein(a), and C-reactive protein (Mintzer et al., 2009). It has been demonstrated that switching patients from carbamazepine to oxcarbazepine causes serum lipids to decline (Isojärvi et al., 1994), and one might expect that switching from carbamazepine to ESL would have a similar effect, although this remains to be demonstrated directly.

The major limitation of the study is the limited sample size of the subgroups. While the overall cohort was substantial in size, with over 1000 drug-treated subjects, dividing the cohort by ESL dose, by use of EIAEDs, and by use of statins produced subgroups of as few as 8-10 patients. More focused study of some of these subgroups (particularly patients taking statins and not taking EIAEDs) is warranted in order to confirm our findings. In fact, among the statin-treated patients, there was no indication of any clear or consistent dose-dependent and clinically significant effects of ESL on serum lipid concentrations.

Another limitation is the relatively short observation period of 12 weeks. It remains uncertain whether longer durations of treatment with ESL might have a different impact on serum lipids; this could be larger (if the time to maximal drug effect is longer than the study duration) or smaller (if an early effect is subsequently reversed by a homeostatic mechanism). However, neither of these possibilities is likely, as the effects of AEDs on the CYP450 system are rapid, and changes in serum lipids occur within 6 weeks of initiation of AED therapy and remain stable over the longer term (Mintzer et al., 2016). With regard to other potential limitations, the analyses are exploratory in nature, so no adjustment for multiplicity was performed. Instead, we evaluated individual comparisons to determine whether they fitted a plausible pattern. Another limitation is that the analyses used a proxy indicator of concomitant statin use. Although it is unlikely that patients’ use of statins would have changed during the 14-week trials, the information on use of statins was for the baseline period only. Consequently, changes in statin use in individual patients during the double-blind period cannot be excluded as potential confounding factors. We also did not account for the various statins and the spectrum of dosing of these agents in our analyses, as this would have resulted in even smaller subgroups that would not have been amenable to analysis. Directed interaction studies in patients not taking EIAEDs, and with individual statins at specific dosing levels, would provide the best test of whether or not use of ESL leads to changes in serum lipid concentrations. Finally, it is important to bear in mind that the current analyses are post-hoc analyses, and as such are subject to a number of potential biases. Directed prospective studies of ESL–statin interactions would provide higher-level evidence to answer these questions, although, clearly, any such studies should use clinical outcome measures (e.g. lipid levels) rather than pharmacokinetic measures.

5. Conclusions

In summary, we find that adjunctive treatment with ESL led to modest effects on serum lipids that were unlikely to be clinically significant. Our data also suggest that pharmacokinetic interactions between ESL and various statins may not have clinically significant pharmacodynamic effects. While further study is required, our findings suggest that ESL might be used safely and without complications in patients who are receiving statin therapy for hyperlipidemia.

Disclosures

SM has received speaker’s honoraria and research support from UCB, and consultancy fees from UCB, Eisai, and AbbVie.

RTW has received compensation for participation in scientific advisory boards or consultancies from UCB Pharma, Eisai, Upsher-Smith, Sunovion, Lundbeck and GLG, and has received speaker’s honoraria from Cyberonics, Sunovion, Lundbeck, Eisai, and UCB Pharma.

JBR has served on scientific advisory boards for Sunovion and Eisai, has received speaker’s honoraria from Sunovion, UCB and Eisai, and has received research support from Sunovion, UCB, Marinus, Eisai, Pfizer and SK Life Sciences.

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PSS and JM are employees of BIAL – Portela & Cª., S.A.

YL, DB and TG are employees of Sunovion Pharmaceuticals Inc.

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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