Brief Communication

Association Between Atorvastatin Exposure and Low Folate Status: A Case–Control Study

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ABSTRACT

Objective: The objective of this study is to assess the association between exposure to atorvastatin (ATV) and low-plasma folate (PF) status. **Methods:** The sample consisted of patients admitted to the internal medicine service of a basic general hospital, located in Zaragoza (Spain). We adopted a pharmacoepidemiological case–control study design. For this, the number of treatment days (TDs) of all the drugs part of their treatment during the study period was obtained from each patient in the sample. The cases were comprised by the number of patient's TDs for which PF ≤3 mg/dl and the controls by the number of patient's TDs for which PF >3 mg/dl. To measure the strength of the association, the odds ratios (ORs) were calculated. The Chi-square test, using the Bonferroni correction, was used to calculate the statistical significance. **Findings:** The sample consisted of 640 polymedicated patients. The mean PF obtained were 8.0 ± 4.6 mg/dl and 2.1 ± 0.6 mg/dl, for the cases and controls, respectively; the total number of TDs for the cases and controls were 7615 and 57899, respectively. We obtained a U-shaped curve when representing the dose of ATV against the corresponding ORs when comparing cases with control. **Conclusion:** Exposure to ATV at 10 or 80 mg is associated with an augmented risk of low folate status. We recommend implementing guidelines for mandatory folic acid fortification in patients exposed to ATV doses of 10 or 80 mg.

KEYWORDS: *Atorvastatin, case–control, folate*

INTRODUCTION

We know that a deficiency of folic acid may result in an elevated risk of cardiovascular diseases,[1] stroke,[2] and/or depression.[3] Furthermore, folate status can be altered in patients with statin treatment, for example, atorvastatin (ATV) compared with the patients not receiving statin therapy. However, current conclusions, based on data obtained by different authors, do not always agree.[4,5] Therefore, complementary studies are necessary to clarify the influence of statins on folate homeostasis. Based on the above, we assessed the association between exposure to ATV and low folate status.

METHODS

The sample consisted of patients admitted to the internal medicine service of a basic general hospital. Those patients were in previous or current treatment with medications that altered plasma folate (PF) values (e.g., folate, phenytoin, sulfasalazine, or trimethoprim with sulfamethoxazole) and/or with diseases that occur with variations in the level (e.g., celiac disease, Crohn's disease, excessive alcohol consumption, hemolytic anemia, and/or kidney dialysis), were excluded. The main variable was PF, as a marker of folate status. We adopted a pharmacoepidemiological case–control study design. As the study took place in a Spanish public hospital, no ethics committee review was required. However, this study did meet the ethical standards of the Helsinki Declaration of 1975, as revised in 2013. For this, the number of treatment days (TDs) of all

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the drugs part of their treatment during the study period was obtained from each patient in the sample. The cases were comprised by the number of patient's TDs for which PF ≤3 mg/dl and the controls by the number of patient's TDs for which PF >3 mg/dl. The data, collected during 2018 and 2019 (pre-COVID-19), were obtained from the assisted electronic prescription system and laboratory records of the hospital. Finally, to measure the strength of the association between exposure to ATV and PF level, the odds (ATV exposed vs. ATV not exposed) were calculated in both groups of cases and controls, and finally, the odds ratio (OR) was calculated between both groups, cases versus controls, for each of the doses of ATV used (10, 20, 40, and 80 mg) and for all of them. The Chi-square test, using the Bonferroni correction, was used to calculate the statistical significance of the differences, taking into account that the number of drugs tested was 14 (n = 14; P < 0.05/14 = 0.0036).

Results

The sample consisted of 640 (age = 87 ± 6 years; body mass index = 31.3 ± 2.9 kg/m^2; height = 159 ± 12 cm; weight = 81 ± 18 kg; women 47%) patients, polymedicated (drugs/patient ≥5), in treatment with doses of ATV at doses of 10, 20, 40, or 80 mg, and admitted to the internal medicine service (average stay = 7.5 days) of a basic hospital with fewer than 200 beds. The mean PF obtained was 8.0 ± 4.6 mg/dl and 2.1 ± 0.6 mg/dl, for the cases and controls, respectively; the total number of TDs for the cases and controls were 7615 and 57,899, respectively.

The second and third columns of Table 1 contain the data on the number of TDs of the cases and controls, both exposed and not exposed to ATV, for the four doses (total) of ATV used and for each of them (10, 20, 40, and 80 mg). Finally, the last column shows the OR data between the cases and controls, both for the total dose of ATV and each of them.

Figure 1 illustrates the resulting U-shaped curve when representing the dose of ATV (10, 20, 40, and 80 mg) used (X-axis) against the corresponding OR obtained when comparing cases with controls (Y-axis).

Discussion

This U-shaped curve, suggests that intermediate doses of ATV (20 and 40 mg) are not associated with interferences in folate homeostasis, whereas very low (10 mg) or very high (80 mg) doses are associated with interferences in folate homeostasis.

Indeed, this U-shaped association, as observed for vitamins, at low doses of ATV occurs such as a deficiency of folate to maintain homeostasis. As the dose is increased, homeostasis is achieved and the trough of the U-shaped curve is reached. Finally, as the dose of ATV exceeds the amount required to maintain homeostasis, overdose toxicity may occur. Therefore, adverse effects are seen at both low and high levels.

This nonlinear bidirectional relation deduced from these results could explain the contradictory observations described by different authors depending on the dose and statin used (e.g., deficiency,[6] increase,[4] no effect of statins on folate status[7] and/or slight increase in PF concentration).[8] On the contrary, the alteration of folate homeostasis, and therefore, its status, associated with exposure to ATV constitutes an example of a drug-associated increased risk for some diseases. Indeed, folate deficiency has been associated with additional risk for cardiovascular diseases[1] and depressive disorders.[9] Nonlinear associations between PF with a risk of cardiovascular disease mortality and all-cause mortality[10] have also been described. Finally, some studies have shown that PF significantly reduces the risk of stroke.[11] By the way of a limitation, many researchers warn about the high risk of introducing

Table 1: Data on the number of patient's treatment days corresponding to cases and controls, exposed and not exposed to atorvastatin

Dose (mg)	Cases (ATV/no ATV)	Controls (ATV/no ATV)	OR (*P*)
10	101/7514	495/57404	1.55 (0.001)*
20	113/7502	846/57053	1.01 (0.87)
40	142/7473	1173/56726	0.92 (0.34)
80	259/7356	1578/56321	1.26 (0.0008)*
Total	614/7001	4098/53801	1.15 (0.0018)*

OR=Odds ratio, ATV=Atorvastatin. *P<0.0036

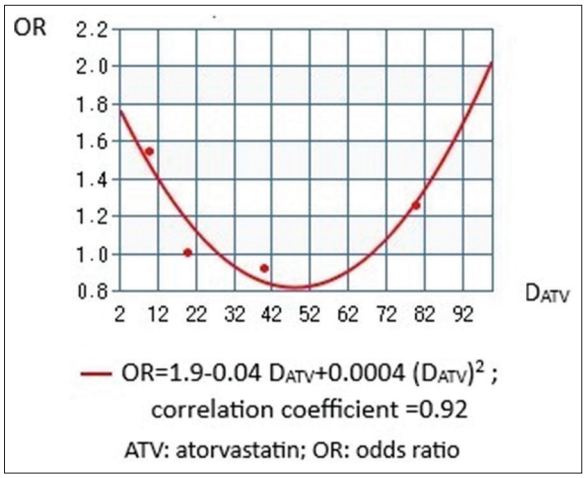

Figure 1: Curve representing the D_{ATV} used (10, 20, 40, and 80 mg; X-axis) against corresponding OR between cases and controls (Y-axis), and best-fitting curve line through the points of a data set. OR: Odds ratio, ATV: Atorvastatin, D_{ATV}: Dose of atorvastatin

biases when using secondary databases such as clinical and therapeutic data extracted from medical records. However, studies based on data drawn from secondary databases do reflect routine clinical practice. Moreover, despite not being used to test hypotheses, they are used to generate them. Further, because we did not assess the influence of age, although all the patients were older than 65 years, the presence of polymorphisms in cytochrome P450, previous outpatient treatments and cotreatments, and other possible hidden covariates could have had an influence.

In short, based on electronic medical and prescription records and administrative databases using a pharmacoepidemiological case–control study, we assessed the influence of ATV exposure and folate status. The results indicated that exposure to ATV at low doses (10 mg) or very high doses (80 mg) is associated with a high risk of the alteration of folic acid homeostasis, and consequently, increased risk of cardiovascular diseases, stroke, and/or depression. We, therefore, recommend implementing or creating guidelines for mandatory folic acid fortification in these cases.

Authors' Contribution

All authors have contributed equally.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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