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ORIGINAL ARTICLE

Baseline ALT levels as a marker of glycemic response to treatment with GLP-1 receptor agonists☆

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GLP-1 receptor agonists;
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Abstract
Background and objectives: This study aimed to assess if ALT levels, as a marker of non-alcoholic fatty liver disease, may predict HbA1c response to treatment with GLP-1 receptor agonists (GLP-1 RAs).
Patients and methods: A retrospective, longitudinal, analytical study was conducted including patients with type 2 diabetes mellitus continuously treated with GLP-1 agonists (85% with liraglutide) for one year. Patients were divided into two groups according to baseline ALT levels, with 24 U/L (the median of the distribution) as the cut-off point. The dependent variable was HbA1c change (one-year follow-up minus baseline).

The predictive value of ALT levels above 24 U/L and ALT change was analyzed using multivariate linear regression adjusted to age, gender, diabetes duration, type and dose of GLP-1 RA, baseline HbA1c, baseline body mass index (BMI), and change in BMI.
Results: A total of 117 patients (48% females) aged 58.6 (SD 9.6) years were enrolled into the study. Treatment was associated with a change in ALT of −4.3 U/L ($p = 0.041$) and a change in HbA1c of −1.1% ($p < 0.0001$). Decreases in HbA1c (−1.41% vs −0.76%; $p = 0.045$) and ALT (−9.25 vs 0.46 U/L; $p = 0.002$) were significantly higher in patients with ALT levels above the median. In the multivariate analysis, both ALT >24 U/L ($b = -0.74$; 95% CI: −1.31 to −0.18; $p = 0.011$) and ALT change ($b = 0.028$; 95% CI: 0.010–0.046; $p = 0.003$), were significant response predictors.
Conclusions: Elevated baseline transaminase values and decreased transaminase levels during follow-up are associated to a favorable glycemic response to GLP-1 RAs.

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PALABRAS CLAVE
Agonistas del receptor de GLP1;
Esteatosis hepática no alcohólica;
Diabetes tipo 2

Niveles de ALT y respuesta hipoglucemiante al tratamiento con agonistas del receptor de GLP-1

Resumen
Antecedentes y objetivo: Evaluar si los niveles de ALT, como marcador de esteatosis hepática no alcohólica, pueden determinar la respuesta hipoglucemiante al tratamiento con agonistas del receptor GLP-1 (AR-GLP1).
Pacientes y métodos: Estudio analítico longitudinal retrospectivo. Se incluyeron pacientes con diabetes tipo 2 (DM2) tratados sin interrupción con AR-GLP1 (85% liraglutida) durante un año. Se clasificó a los pacientes en 2 grupos según niveles iniciales de ALT, con punto de corte en la mediana (24 U/l). La variable dependiente fue el cambio (final-inicial) de HbA1c.

El valor predictivo de niveles de ALT > 24 U/l y del cambio en ALT fue analizado con regresión lineal multivariante ajustada para edad, género, evolución de DM2, tipo y dosis de AR-GLP1, niveles iniciales de HbA1c, índice de masa corporal (IMC) y cambio de IMC.
Resultados: Se incluyeron 117 pacientes (48% mujeres) con edad media de 58,6 (DE 9,6) años. El tratamiento estuvo asociado con un cambio en ALT de −4,3 U/l (p = 0,041) y un cambio en HbA1c de −1,1% (p < 0,0001). Tanto el descenso de HbA1c (−1,41% vs −0,76%; p = 0,045) como el de ALT (−9,25 vs 0,46 U/l; p = 0,002) fueron significativamente más marcados en pacientes con ALT por encima de la mediana. En análisis multivariante tanto niveles de ALT > 24 U/l (b = −0,74; IC 95%: −1,31 a −0,18; p = 0,011) como el cambio en ALT (b = 0,028; IC 95%: 0,010 a 0,046; p = 0,003) fueron factores predictivos de respuesta.
Conclusiones: Niveles elevados de transaminasas y su descenso se asocian a una respuesta hipoglucemiante favorable a AR-GLP1.

Introduction

As the priority in the treatment of type 2 diabetes mellitus (T2DM) is the achievement of good metabolic control as soon and as safely as possible, advances are needed in our understanding of the factors able to predict the response of individual patients to the currently available drugs.[1] Although the study of pharmacogenetic interactions may be a way to achieve personalized treatment in the future,[2] today we need to rely on clinical criteria to select the specific treatment.

GLP-1 receptor agonists (GLP-1 RAs) are widely used in T2DM because of their multiple benefits, including the stimulation of glucose-dependent insulin secretion and the inhibition of glucose-regulated glucagon secretion, the slowing of gastric emptying, and increased satiety.[3] Their use results in blood glucose decrease with no risk of hypoglycemia, decreased body weight, and an improvement in cardiovascular risk factors. The use of GLP-1 RAs in combination with other oral antidiabetic drugs and/or insulin is therefore recommended in international guidelines.[4]

Meta-analyses have shown that HbA1c decreases by approximately 1% after treatment with GLP-1 RAs, but this is a mean effect subject to wide variability.[5] It would therefore be helpful to identify the parameters associated with a favorable response of patients to this drug class.

Since GLP-1 RAs are known to be able to improve insulin resistance in the liver,[6] our hypothesis was that the efficacy of these agents could be increased in the presence of non-alcoholic fatty liver disease (NAFLD). Alanine aminotransferase (ALT) is a marker of NAFLD. In fact, even elevated ALT levels within the normal range have been associated with intrahepatic fat contents.[7]

The objectives of our study, based on the study of a database of patients with T2DM treated with GLP-1 RAs, were as follows:

1. To select a clinical model predicting for a favorable response to treatment with GLP-1 RAs.
2. To assess whether baseline ALT levels, as a marker of NAFLD, were able to predict the response to treatment.

Patients and methods

Design

This was an analytical, retrospective cohort study.

Patients

In 2013, as part of a project led by the Aragonese Society of Endocrinology and Nutrition (SADEN), data started to be collected from patients with T2DM prescribed treatment with GLP-1 RAs by a specialist. This study guarantees patient anonymity and is retrospective in nature. Patients are treated at the discretion of the physician in charge. The base currently includes 356 patients. Hospitals which have contributed to date include: Hospital Miguel Servet (Saragossa), HCU Lozano Blesa (Saragossa), Hospital General