SAFETY AND EFFICACY OF GLP-1 RECEPTOR AGONISTS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND HEPATIC IMPAIRMENT: A PHARMACOLOGICAL REVIEW

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BACKGROUND: Type 2 diabetes mellitus is highly associated with different liver disorders ranging from chronic viral hepatitis to NASH/NAFLD or end stage liver disease. In addition, the use of many antidiabetic agents such as metformin or sulphonylureas in hepatic impairment could be concerning. For this reason, GLP-1 receptor agonists could represent a good therapeutic chance for these patients, especially in NAFLD affected where GLP-1 receptor agonist efficacy clinical trials have shown promising results for the treatment of this untreated condition.

METHODS: We performed an extensive literature search analyzing the most updated evidences regarding PK/PD, safety and efficacy profile of all classes of GLP-1 receptor agonists in patients with T2DM and hepatic impairment.

RESULTS: Regarding pharmacokinetics, just one study has been conducted comparing liraglutide PK of patients with no liver disease vs mild, moderate or severe hepatic impairment. The study showed an overall T max similar in each group (11.3-13.2 h) and a mean AUC (0,∞) progressively decreasing with the increase of liver injury, with a statistically significant relationship with albumin concentration (P=0.041), suggesting that exposure to liraglutide was not increased by hepatic impairment; aim of the study was also to collect safety and laboratory data, indicating no safety concerns1.

Two meta-analysis2-3 on studies conducted before 2015 in patients with T2DM and NAFLD, showed a mean reduction of 12.2 IU/L (95%, CI 4.9-19.4, P<0.001) of ALT concentration with respect to the baseline and a 42% median relative reduction in intrahepatocellular lipid after 6 months treatment with liraglutide or exenatide. In addition it was found that treatment with lixisenatide increased the proportion of patients who achieved normal ALT levels in a comparison with placebo or other glucose-lowering agents, especially in obese patients. More recent studies have demonstrated an effect of GLP-1RA on lipid metabolism and inflammation. In the study conducted by Armstrong et al. patients were randomized to receive liraglutide or placebo for 12-weeks liraglutide highlighting the decrease of hepatic de novo lipogenesis in vivo (-1.26 vs. +1.30%; p<0.05).

Furthermore, an experiment in a mice model of high-fat and high-carbohydrate (HFHC) diet induced HCC demonstrated the suppressive effect of exenatide in diabetes related HCC (a frequent complication of NAFLD) as a result of the inactivation of multiple oncogenes such as EGFR and STAT3.

Our review suggests a potential beneficial role of GLP-1 receptor agonists in patients with T2DM and hepatic disease.

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