Could favorable effects of liraglutide on steato-hepatitis be independent of weight loss in type 2 diabetes ? A case report.

C. GARCIA, L. BORDIER, O. DUPUY, H. MAYAUDON

French Military Hospital BEGIN
Endocrinology department
69 avenue de Paris - 94160 SAINT MANDE - FRANCE

Introduction :

Some data suggest a favorable effect of Glucagon-Like Peptide-1 (GLP-1) on steato-hepatitis (SH) in type 2 diabetes. We report here a case of improvement of SH in a patient treated by liraglutide, suspected to be independent of weight loss.

Patients and methods:

A 31 year-old woman presented type 2 diabetes. Her weight was 80 kg for 1.58m (BMI=32 kg/m²). A treatment by liraglutide was initiated at 1.2 mg per day, percutaneously. A regular follow-up was performed with the recording of weight, HbA1c, iron and lipid status. Liver function was regularly assessed by liver enzymes dosage and a FIBROMAX® score establishment.

The spectaculary results obtained led to initiate an observational and prospective study in other patients whose diabetes was thought to require liraglutide, and for whom the same protocol of clinical and biological follow-up was applied. Then 11 type 2 adult diabetic patients including this woman were included. Data were compiled before and after one year of treatment by liraglutide. For statistical analyses a wilcoxon matched-pairs signed rank test was used ; $p<0,05$ was considered significant. Statistical analyses were performed with GraphPad Prism® software.

Results :

For the 31 year-old woman, and before liraglutide initiation, HbA1c was 8.6%, ASAT 45IU/L, ALAT 58 IU/L, GGT 174IU/L. After only 3 months HbA1c dropped to 6.5%, ASAT 42IU, ALAT 52IU, GGT 92IU/L, as her weight was still 79.4 kg. At 1 year the results were: HbA1c 6.7%, ASAT 17 IU/L, ALAT 18 IU/L and GGT 26 IU/L. Triglycerides level decreased from 2.63 to 0.8 mmol/L. The FIBROMAX score indicated initially an important SH, which greatly improved at one year (Steatotest=1 vs 3, Nashtest=1 vs 2, Actitest=0 vs 1 to 2), while her weight was 74kg.

For the 11 patients, the values of the longitudinal follow-up containing FIBROMAX score, weight, HbA1c, ASAT, ALAT before and one year after treatment are mentionned in the figures below.

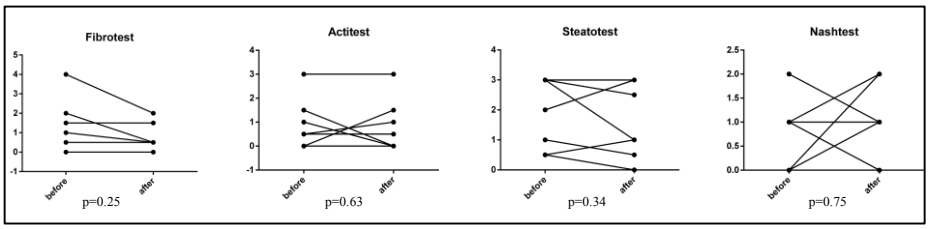

Fig.1: Evolution of the FIBROMAX® score obtained for 11 patients before and 1 year after the introduction of liraglutide at the dose of 1.2mg/day.

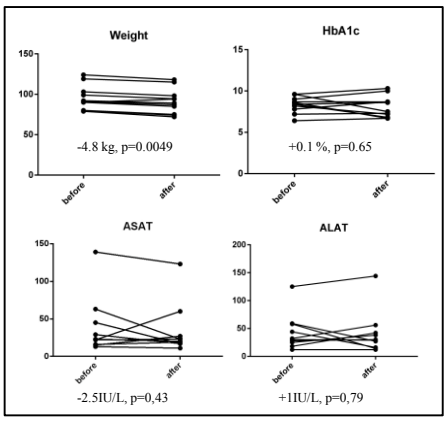

Fig.2: Evolution of weight, HbA1c, ASAT and ALAT in 11 patients before and one year after the introduction of liraglutide, at the dose of 1,2 mg/day.

The analyse of the different parameters of the FIBROMAX score showed a trend for a favorable effect of liraglutide in steatosis and non alcoolic steatohepatitis, but this tendency did not reach significance (fig.1). Some patients did respond to the treatment, others did not, and some patients escaped very clearly.
The 11 patients for whom the data could have been collected lost weight (median – 4.8kg), and this was statistically significant (fig.2, p=0.0049). However some patients were non-responders in terms of glycaemia. A favorable trend for ASAT were also observed, but this was not statistically significant.

The FIBROMAX® score is designed to assess the degree of liver fibrosis, activity, steatosis and SH associated with chronic liver diseases like C hepatitis or metabolic diseases.

Beneficial effects of GLP-1 analogs on SH are documented in some animal models for few years. Ding (1) showed that exendin-4 improved SH in *Ob/Ob mouse,* but in this study, rodents lost weight as well and results were not adjusted to weight loss. This author showed also that this GLP-1 analog could directly act on hepatocytes by activating the cAMP pathway, leading to a decrease of fatty acids synthesis, probably by beta-oxydation activation, and triglycerides storage inhibition in hepatocytes. Furthermore, an additional effect of exendin-4 in association with pioglitazone was demonstrated in the decrease of hepatic steatosis in diabetic patients as compared to a group of patients treated by pioglitazone alone (2).
A study performed in C57BL/6J mice showded similar results with liraglutide, which seemed to have protective effects on hepatic steatosis induced by a high fat and fructose diet (3). In man, Jendle suggested a reduction of hepatic steatosis with liraglutide at 1.8mg/day in type 2 diabetic patients by considering the liver to spleen attenuation measurement obtained by computed tomography (4). However these values were not adjusted on weight loss.

The observation of our first patient suggested a beneficial role of liraglutide on SH. Proving that these results could be independent of weight loss was difficult. At 3 months Nashtest decreased to the value of 1, as her weight remained stable. This effect could be independent of weight loss as biological parameters including ASAT, ALAT and GGT improved at only 3 and 6 months while she did not loose weight yet. At one year the parameters of the FIBROMAX® score improved, liver enzymes were normalised, but the patient lost 6 kg by comparaison with first evaluation. The results obtained here in the group of diabetic patients were however non significant, probably in part because of the low number of patients included, and it is actually still difficult to answer clearly to this question. The patients included here could have a non-responder profile to liraglutide, as HbA1c did not decrease significantly at one year.

Conclusion:

This work is the first study designed to use the FIBROMAX® score in the assessment of liraglutide in steatosis and non alcoolic steato hepatitis associated with type 2 diabetes, mostly assessed by ultrasound or liver to spleen attenuation measured on computed tomography. The low power of this study could explain why we could not demonstrate a favorable effect of GLP-1 analog in this series of type 2 diabetes patients. Furthermore we suggest that there are responders and non responders to the drug at the level of the liver target. The LEAN study will try to answer this question. In this ongoing prospective study, liver biopsies will be analysed in the evaluation of hepatic steatosis and steatohepatitis before and after the use of liraglutide (5). Pharmacogenomic studies will probably be useful to better determine which patients could be responders to liraglutide at the hepatic level.

References :

1. Ding X, Saxena NK, Lin S, Gupta N, Anania FA. Exendin-4, a glucagon-like protein-1 (GLP-1) receptor agonist, reverses hepatic steatosis in *Ob/Ob* mice. Hepatology, 2006;43:173-181.
2. Samson SL, Sathyanarayana P, Jogi M, Gonzalez EV, Gutierrez A, Krishnamurthy R et al. Exenatide decreases fibroblast growth factor21 resistance in non-alcoolic fatty liver disease in mouse model of obesity and in a randomised controlled trial. Diabetologia, 2011;54:3093-3100.
3. Mells JE, Fu PP, Sharma S, Olson D, Cheng L, Handy JA et al. GLP-1 analogue, liraglutide, ameliorates hepatic steatosis and cardiac hypertrophy in C57BL/6J mice fed a western diet. Am J Physiol Gastroentest Liver Physiol, 2012;302:G225-35.
4. Jendle J, Nauck MA, Matthews DR, Frid A, Hermansen K, Düring M et al. Weigth loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of reduction in fat tissue. Diabetes, obesity and metabolism, 2009;11:1163-1172.
5. Armstrong MJ, Barton D, Gaunt P, Hull D, Guo K, Stocken D. Liraglutide efficacy and action in non-alcoholic steatohepatitis (LEAN): study protocol for a phase II multicentre, double-blinded, randomised, controlled trial. BMJ Open 2013;3:e003995. doi:10.1136/bmjopen-2013-003995.