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# Insulin-like growth factor I (IGF-I) replacement therapy increases albumin concentration in liver cirrhosis: Results of a pilot randomized controlled clinical trial☆

Mariam Conchillo[1], Robert J. de Knegt[2], Marina Payeras[1], Jorge Quiroga[1], Bruno Sangro[1], Jose-Ignacio Herrero[1], Inma Castilla-Cortazar[1], Jan Frystyk[4], Allan Flyvbjerg[4], Carl Yoshizawa[3], Peter L.M. Jansen[2], Bruce Scharschmidt[3], Jesús Prieto[1,*]

[1]*Department of Medicine and Liver Unit, Clinica Universitaria, Medical School and Center for Applied Medical Research (CIMA), University of Navarra, Pamplona, Spain*

[2]*Department of Gastroenterology and Hepatology, University Hospital, Groningen, The Netherlands*

[3]*Chiron Corp. Emeryville, CA, USA*

[4]*The Medical Research Laboratories, Clinical Institute, Aarhus University Hospital, Aarhus C, Denmark*

***Background/Aims*: Insulin-like growth factor I (IGF-I) is an anabolic hormone synthesized in the liver whose levels decrease sharply in liver cirrhosis.**

***Methods*: We conducted a randomized double-blind placebo-controlled clinical trial to evaluate the effect of subcutaneous administration of IGF-I (20 μg/kg/day with dose escalation to 50–100 μg/kg/day) for 4 months in patients with alcoholic or primary biliary cirrhosis (PBC) and subnormal IGF-I levels. Eight alcoholics and one PBC entered the placebo group and seven alcoholics and two PBC the treatment group. Biochemistry, body composition, muscle mass and strength, and resting energy expenditure (REE) were evaluated.**

***Results*: Total serum IGF-I and IGF-I/IGFBP-3 ratio (a surrogate marker of IGF-I biovailability) increased in the treatment group but IGF-I values still remained below normal limits in the treated patients. No differences were observed in body composition, muscle strength or muscle mass between groups. However, IGF-I therapy increased significantly serum albumin ($P=0.038$) and this improvement correlated positively with variation of IGF-I/IGFBP-3 ratio. IGF-I treatment also tended to increase REE ($P=0.085$); this difference was significant ($P=0.049$) in the subgroup of alcoholic patients.**

***Conclusions*: A short course of IGF-I increased albumin levels and tended to improve energy metabolism in liver cirrhosis. These findings warrant larger clinical trials to assess the clinical benefit of IGF-I in cirrhotic patients.**



***Keywords*: Liver cirrhosis; Liver function; Nutrition; Body composition; Resting energy expenditure; IGF-I; IGFBP3; Child–Pugh score**

## 1. Introduction

Hepatocytes are the main source of circulating insulin-like growth factor-I (IGF-I), a potent anabolic hormone whose secretion is stimulated by growth hormone (GH) [1,2]. IGF-I circulates bound to 6 different IGF binding proteins (IGFBP-1 to −6), interacts with specific receptors on target tissues (bone, intestine, testis, muscle, etc) and also acts on hypothalamus to suppress GH

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* Corresponding author. Tel./fax: +34 948 296785.

*E-mail address:* jprieto@unav.es (J. Prieto).

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secretion [3–5]. The liver is also the major producer of IGFBPs, mainly IGFBP-1 and IGFBP-3. IGFBP-3 sequesters IGF-I in the vascular system, increasing its half-life and providing an IGF-I reservoir. The ratio of total IGF-I/IGFBP-3 is considered as a surrogate index of IGF-I bioavailability [5].

In subjects with liver cirrhosis plasma levels of total IGF-I, free IGF-I and IGFBP-3 are decreased while GH is increased, indicating resistance to GH and reduced hepatic functional reserve [6–8]. Liver cirrhosis is, therefore, an IGF-I deficiency state, the severity of which correlates with the progression of the liver disease [6–10]. Indeed, many of the clinical features of advanced cirrhosis such as malnutrition, muscle wasting, loss of bone mass, and hypogonadism could be ascribed to deficient IGF-I anabolic activity. The possible therapeutic use of IGF-I in liver cirrhosis is supported by studies in cirrhotic rats demonstrating that IGF-I replacement therapy (20 μg/kg): (a) increases food intake, nitrogen balance and food efficiency [11]; (b) enhances intestinal absorption of glucose and aminoacids [12]; (c) increases bone density [13]; (d) corrects hypogonadism [14]; (e) diminishes oxidative liver damage [15]; (f) improves liver function [15] and (g) decreases liver fibrogenesis [15].

Based on these premises we decided to perform a small controlled clinical trial to evaluate the effects of IGF-I replacement therapy in patients with liver cirrhosis of non-viral origin. Because of the reported growth-promoting and antiapoptotic properties of IGF-I, in this pilot study we excluded cirrhotic patients with higher risk of cancer development such as those with haemochromatosis or chronic hepatitis B or C virus infection.

## 2. Materials and methods

We designed a randomized, double-blind, placebo controlled pilot study to investigate whether IGF-I replacement therapy could benefit cirrhotic patients. The study was performed in two centers: Clinica Universitaria of Navarra (Spain) and University Hospital Groningen (The Netherlands).

### 2.1. Patient selection and eligibility

Patients were males or females aged 18–70 years with alcoholic cirrhosis (with at least 3 months of abstinence as assessed by patient's interview) or primary biliary cirrhosis, plasma IGF-I levels below the lower age-adjusted 5th percentile (two standard deviations below the age-adjusted normal level) and willing and able to give written informed consent to participate in the study.

The exclusion criteria were: etiologies other than alcohol or primary biliary cirrhosis, tense ascites requiring repeated paracenteses, severe peripheral edema, hospitalization for gastrointestinal bleeding, spontaneous bacterial peritonitis or other life-threatening complications within 3 months of entering the study, encephalopathy requiring protein restriction or precluding collaboration, drug abuse, hematocrit $\leq 28\%$, creatinine $>$ 2 mg/dl, serum sodium $\leq 125$ mmol/l, bilirubin $\geq 10$ mg/dl, prothrombin time $\geq 10$ s prolonged, PSA $\geq 4$ μg/l, α-fetoprotein $\geq 10$ μg/l or mass lesion on abdominal ultrasound within 3 months before entering the study, clinical conditions that would compromise exercise testing, past or present history of malignancy within the last 10 years with the exception of curatively treated basal cell carcinoma, anti-diabetic therapy, proliferative retinopathy and coexistence of any other diseases or medication which might interfere with the assessment of nutritional status. Usual therapy of the complications of cirrhosis such as neomycin, lactulose, lactitiol, diuretics and propanolol were allowed.

## 3. Study design

The patients were randomized to receive human recombinant IGF-I (Chiron Corp., Emeryville, CA, USA) or placebo for 120 days. We used a 1:1 randomization with a block size of 2. The randomization was stratified by investigative site and etiology. The starting dose of IGF-I was 20 μg/kg administered as a single subcutaneous injection within 60 min after breakfast. The dose was selected based on preclinical data showing beneficial effects and absence of hypoglycemia with this dose in cirrhotic rats [11–15]. Study subjects remained in the hospital the first day for observation and instruction on self-injection and monitoring the blood glucose every 4 h. The dose was adjusted according to plasma levels of total IGF-I measured in the out-patient clinic at 09.00 h (prior to that day's IGF-I dose) weekly during the first month. A normal IGF-I level was defined as a concentration within 1 SD of the normal level adjusted for age. If total IGF-I level was low, the dose was increased at increments of 5–10 μg/kg/day up to a maximal dose of 50 μg/kg/day (Pamplona cohort) or 100 μg/kg/day (Groningen cohort). Patients in the placebo group received subcutaneous vehicle (sodium succinate, pH 6). The dose of placebo was adjusted in the same way as that of IGF-I. IGF-I values were made available to only one investigator in each center who was responsible for adjusting the dose of IGF-I and who did not participate in patient's evaluation. All other investigators involved were blinded.

The following parameters were analyzed at baseline and at the end of the study period: levels of total and free IGF-I, IGFBP-3, liver biochemistry, muscle mass (quadriceps on dominant side of the body by CT scan), muscle strength (isokinetic exercise of quadriceps on dominant side), body composition by dual-energy-X-ray-absorptiometry (DEXA), respiratory quotient and resting energy expenditure (indirect calorimetry) and assessment of the quality of life (SF-36 questionnaire). Quadriceps muscle mass and strength as well as lean body mass were selected as the primary efficacy measures. Fat mass, bone mineral density, liver function tests, Child–Pugh score, respiratory quotient, resting energy expenditure and quality of life were secondary end points.

## 4. Determinations

Serum concentration of total and free IGF-I and IGFBP-3 were determined as previously reported [16]. Muscle mass was measured using CT-scan (SOMATON PLUS 4. Siemens, Forcheim, Germany) [17]. CT of the dominant

quadriceps muscle was performed and the midpoint between the great trochanter and lateral joint line of the knee. Slice thickness was 10 mm. The CT scans were evaluated three times and the mean value was recorded. Upper leg muscle strength was measured as peak torque of flexion (hamstrings) and extension (quadriceps) at the knee using an isokinetic dynamometer (Enraf Nonius B.V., Delft, The Netherlands). The dominant leg was tested with standardized procedures as described elsewhere [18]. The speeds were 30, 90 and 120 (degrees/second).

Resting energy expenditure was measured by indirect calorimetry using a ventilated hood system (VMAX 29 SENSOR, Medics Corporation, Yorba Linda, CA, USA). Measurements were performed in early morning after overnight fast and half an hour in recumbency. The system was calibrated before measurements. Respiratory quotient (RQ) was determined (RQ = VCO2/O2) and resting energy expenditure (REE) was calculated according to the equation of Ferranninni [19] and measured REE was compared to predicted REE according to the equations of Harris-Benedict [20]. Body composition analysis was performed by DEXA using a QRD-4500W (Hologic, Inc., Waltham, MA, USA). The subject was placed in supine position on a scan table for 15 min while DEXA scan performed multiple, fast-speed transverse scans from head to toes with 1 cm intervals. Data were collected in maximal 205 scan lines $\times$120 sample points (pixel size: 4.8$\times$9.6 mm). Total tissue mass, bone mineral mass, fat mass, and lean tissue were derived according to computer algorithms (Hologic software) provided by the manufacturer.

## 5. Ethics

The study was approved by the Ethic's Committees of University Hospital of Navarra (Spain) and University Hospital Groningen (The Netherlands). Patients entered after written and informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki (1964), as revised in 1996 and with ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and the Spanish Royal Decree (Real Decreto 561/1993).

## 6. Data analysis

Differences between values at day 120 and at day 0 ($\Delta$) were compared between groups. Two-sided exact $P$-values were calculated using the Mann–Whitney–Wilcoxon test. Correlation coefficients were calculated using Spearman's method. Statistical significance was defined as a $P$ value $<0.05$. Since alcoholic and primary biliary cirrhosis are pathogenetically different and alcoholic patients constituted the great majority of those included in the study, a second analysis in the subgroup of patients with alcoholic cirrhosis was performed.

## 7. Results

Between September 2001 and December 2002, 30 consecutive patients were assessed for eligibility. Of these, seven did not meet the inclusion criteria and three refused to participate. Twenty patients were randomized to receive placebo (nine patients) or IGF-I (eleven patients). Fifteen patients were included in Pamplona and five in Groningen. Neither dropouts nor exclusions occurred in the placebo group. In the treatment arm, one patient was lost to follow up because he underwent liver transplantation before the final evaluation, and one patient was excluded from the analysis because of interruption of alcohol abstinence. Therefore, the final statistical evaluation included nine patients in the control group (eight with alcoholic cirrhosis) and nine patients in the treated group (seven with alcoholic cirrhosis). The patient characteristics were generally well matched at baseline, as shown in Table 1, although albumin levels tended to be lower in the subjects randomized to IGF-I treatment. On baseline, the mean doses of spironolactone ($P=0.796$) furosemide ($P=0.863$) and propranolol

**Table 1**
**Clinical and biochemical findings in treated patients and controls at baseline**

| | IGF-1 | Placebo |
|---|---|---|
| M/F | 6/3 | 7/2 |
| Age | 53 (37–65) | 58 (46–67) |
| Ethanol/CBP | 7/2 | 8/1 |
| Child–Pugh score | 7.8 ± 1.6 | 7.0 ± 1.0 |
| Total IGF-1 (μg/L) (*78–258*) | 33.8 ± 13.2 | 37.3 ± 10.3 |
| Free IGF-1 (μg/l) (*0.18–0.84*) | 0.10 ± 0.08 | 0.10 ± 0.08 |
| IGFBP-3 (μg/l) (*2020–4310*) | 1076 ± 406 | 1063 ± 356 |
| IGF-1/IGFBP3 | 0.03 ± 0.01 | 0.04 ± 0.01 |
| Total bilirubin (*0.2–1.2* mg/dl) | 4.0 ± 1.9 | 4.3 ± 2.2 |
| Albumin (3.5–5 g/dL) | 3.2 ± 0.5 | 3.6 ± 0.4 |
| Prothrombin time (11–15 s) | 15.2 ± 1.9 | 15.8 ± 1.9 |
| ALT (*<29* IU/l) | 34 ± 22 | 26 ± 12 |
| AST (*<22* IU/l) | 45 ± 34 | 42 ± 23 |
| Total protein (*6.6–8.7* g/dl) | 6.4 ± 1.4 | 6.8 ± 0.7 |
| Alk. phosphatase (*73–207* IU/l) | 313 ± 256 | 214 ± 87 |
| GGT (*8–38* IU/l) | 66 ± 44 | 81 ± 63 |
| Resting energy expenditure (REE) (Kcal/day) | 1672 ± 323 | 1760 ± 388 |
| REE percentage | 106 ± 14 | 112 ± 15 |
| Previous encephalopathy (number of patients) | 3 | 2 |
| Muscle mass (cc) | 64.6 ± 13.9 | 67.6 ± 12.0 |
| Muscle strength 30° ext (Nm/kg) | 1.5 ± 0.6 | 1.3 ± 0.3 |
| Lean body mass (kg) | 53.1 ± 10.9 | 53 ± 9.5 |
| Fat mass (kg) | 22 ± 10.7 | 21.9 ± 6.6 |
| Bone mineral mass (kg) | 2.2 ± 0.5 | 2.2 ± 0.6 |

Normal values are shown in italics. Subject values are shown as mean and range or SD.

**Table 2**
**Differences (Δ) between absolute values at day 120 and day 0 of the study**

| Δ (Delta value) | IGF-I | Placebo | *P* |
|---|---|---|---|
| Total IGF-1 (μg/L) | 13.3±19.5 | −3.3±8.6 | 0.024 |
| Free IGF-1(μg/L) | 0.02±0.10 | 0±0.10 | ns |
| IGFBP-3 (μg/L) | −96.8±155.8 | 21.7±155.7 | ns |
| IGF-1/IGFBP-3 | 0.020±0.000 | −0.004±0.000 | 0.0001 |
| Total bilirubin (mg/dl) | 0.3±1.5 | −0.6±1.1 | ns |
| Albumin (g/dl) | 0.2±0.3 | −0.1±0.3 | 0.038 |
| Albumin alcoholic cirrhosis ($n=15$) | 0.4±0.3 | −0.2±0.4 | 0.014 |
| Prothrombin time (sc) | 0.6±1.9 | −0.1±1.5 | ns |
| Child–Pugh score | −0.6±0.8 | 0±0.7 | 0.113 |
| Child–Pugh score, alcoholic cirrhosis ($n=15$) | −0.9±0.9 | −0.1±0.6 | 0.072 |
| ALT (IU/L) | −5.±14 | −1±6 | ns |
| AST (IU/l) | 1±21 | −3±5 | ns |
| Total protein (g/dl) | 0.2±0.9 | −0.1±0.5 | ns |
| Alkaline phosphatase (IU/l) | 3±47 | −6±38 | ns |
| GGT (IU/l) | 8±42 | 14±43 | ns |
| Respìratory quotient | −0.03±0.00 | 0.02±0.10 | ns |
| Resting energy expenditure (REE) (Kcal/day) | 201±160 | 46±208 | 0.094 |
| Resting energy expenditure (REE) (Kcal/day) alcoholic cirrhosis ($n=15$) | 206±90 | 19±205 | 0.054 |
| REE percentage | 12.5±11.4 | 3.1±12.5 | ns |
| Fat mass (kg) | −0.02±1.6 | 0.70±1.20 | ns |
| Bone mineral mass (kg) | −0.02±0.07 | 0±0.04 | ns |
| Lean body mass (kg) | 0.5±2.9 | −0.7±1.8 | ns |
| Muscle strength 30° ext (Nm/kg) | 0.03±0.30 | 0.10±0.20 | ns |
| Muscle mass (cc) | 0.0±3.9 | 0.1±3.5 | ns |
| SF-36 questionnaire[a] | | | |
| Physical function | 7.2±11.2 | 16.6±9.3 | 0.050 |
| General health | −3.0±17.9 | 11.4±13.0 | 0.031 |
| SF-36 questionnaire[a] (alcoholic cirrhosis) | | | |
| Physical function | 7.8±12.5 | 16.2±9.9 | ns |
| General health | −2.4±20.4 | 12.8±13.1 | ns |

[a] Higher score indicates better performance.

($P=0.863$) were similar in both groups and during the study period there were no differences between groups in delta values of the doses of these drugs ($P=0.436$, $P=0.436$ and $P=0.730$ for spironolactone, furosemide and propranolol, respectively).

### 7.1. Effects on IGF-I and IGFBP-3

IGF-I treatment did not result in significant differences between groups either in free IGF-I or in IGFBP-3 levels (Table 2), but total serum IGF-I and the IGF-I/IGFBP-3 molar ratio (which is considered to reflect IGF-I bioavailability) increased during therapy in the treated group as compared to patients who received placebo (Fig. 1). At the doses of IGF-I used in this study the median values of total IGF-I, free IGF-I and IGFBP-3 in the treated patients still remained below normal levels (see normal age-adjusted values in Table 1) (Fig. 1).

### 7.2. Adverse events

The treatment was well tolerated. No hypoglycemic episodes occurred during the study. Adverse events recorded during the trial are summarized in Table 3. One patient in the IGF-I group was diagnosed 15 days after completion of the therapy of a small tumor in the left upper jaw (poorly differentiated squamous cell carcinoma). This patient had noticed the lesion before therapy but did not mention it to the clinician when she was investigated for inclusion in the trial. After this incident, regular ear-nose-throat examination was incorporated into the protocol. One patient in the placebo group developed multifocal hepatocellular carcinoma 6 months after completion of the trial. None of the treated patients developed liver cancer during follow-up. Also it should be noted that none of the patients on IGF-I developed encephalopathy during treatment, although 3 subjects assigned to this group had pre-existing encephalopathy, whereas two of the placebo group had encephalopathic episodes during the study.

### 7.3. Effects of primary and secondary end-points

These effects are summarized in Table 2. No differences between groups were observed with respect to body composition, muscle mass or muscle strength. There was a trend for increased lean body mass in the IGF-I treated

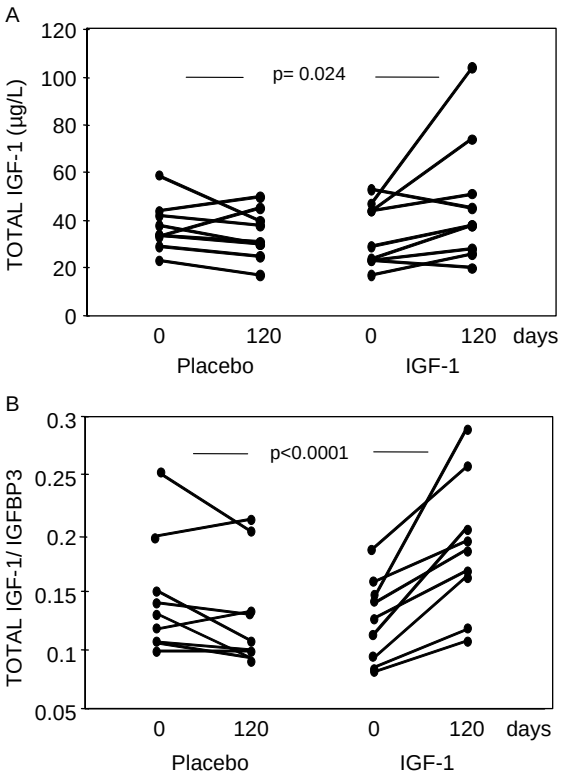


**Fig. 1. Plasma levels of total IGF-I (A) and IGF-I/IGFBP-3 molar ratio (B) in patients receiving placebo or IGF-I before (day 0) and at the end of the study (day 120). Blood samples were obtained 24 h after IGF-I administration. The delta value of each case (day 120 − day 0) was used for comparison between groups. Normal values of total IGF-I in the age range of 40–70 years are 78–258 ng/ml.**

group as compared to controls. Serum albumin increased significantly ($P=0.038$) in IGF-I treated patients relative to subjects receiving placebo (Table 2 and Fig. 2). In all patients, the change in albumin levels during the study correlated positively and significantly with the variation in the IGF-I/IGFBP-3 ratio ($r=0.56$; $P=0.015$). No differences were observed in the remaining liver function tests. There was a trend toward improvement of Child–Pugh score ($P=0.113$) and toward increasing REE ($P=0.094$) in the IGF-I group relative to placebo. Since the Pamplona patients (6 on IGF-I and 7 on placebo) received a lower

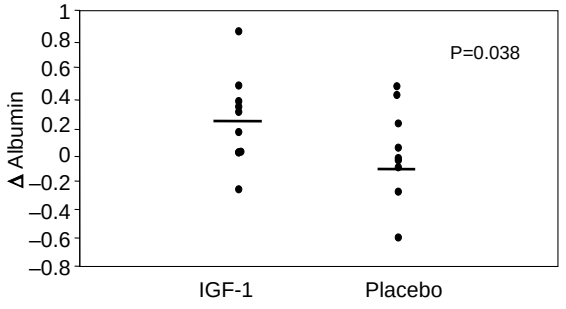


**Fig. 2. Delta albumin (value at day 120 − value at day 0) in patients receiving placebo or IGF-I.**

**Table 3**
**Adverse events in patients treated with IGF-1 or placebo**

| Adverse effects | IGF-1 | Placebo |
|---|---|---|
| Abdominal hematoma | 2/9 | 2/9 |
| Dizziness | 1/9 | 3/9 |
| Rectal bleeding | 0/9 | 1/9 |
| Influenza | 1/9 | 2/9 |
| Xerostomia | 1/9 | 0/9 |
| Myalgia | 1/9 | 0/9 |
| Muscle cramps | 1/9 | 0/9 |
| Diarrhea | 1/9 | 2/9 |
| Headache | 1/9 | 0/9 |
| Dysuria | 0/9 | 1/9 |
| Vomiting | 0/9 | 1/9 |
| Encephalopathy | 0/9 | 2/9 |
| Arthralgia | 1/9 | 0/9 |
| Hyperglycemia | 0/9 | 1/9 |
| Nausea | 0/9 | 1/9 |

daily dose of IGF-I (50 µg/Kg) this cohort was analyzed separately. In these patients, we observed a significant difference in the delta values of serum albumin ($P=0.014$), and a trend to improvement in the Child-Pugh score ($P=0.051$) and REE ($P=0.101$) favoring IGF-I therapy with respect placebo, similarly to findings in the total group of patients.

In all patients REE correlated significantly with muscle strength (dynamometry), lean body mass (DEXA) and muscle mass (TC) both at baseline ($r=0.49$, $P=0.035$; $r=0.77$, $P<0.0001$ and $r=0.66$, $P=0.003$, respectively) and at day 120 ($r=0.67$; $P=0.002$, $r=0.63$; $P=0.004$ and $r=0.56$; $P=0.015$, respectively). Finally, the SF-36 questionnaire, which analyzes eight variables (physical function, social function, limitations due to physical and emotional problems, mental health, energy, pain, general health), revealed that patients on IGF-I had less marked improvement than patients on placebo for both, general health ($P=0.031$) and physical function ($P=0.05$) (Table 2).

### *7.4. Subgroup of patients with alcoholic cirrhosis*

The improvement in serum albumin after IGF-1 therapy was more evident in patients with alcoholic cirrhosis (Table 2) where, in addition, differences in REE ($P=0.054$) and in the Child–Pugh score ($P=0.072$) approached statistical significance, and no differences in the quality of life test were observed (Table 2).

## 8. Discussion

Since IGF-I displays potent anabolic activities and its levels decrease markedly in liver cirrhosis, we tested the concept that IGF-I supplementation might benefit cirrhotic patients. Because the present study was the first trial administering IGF-I to patients with cirrhosis, entry criteria were stringent and the dose of IGF-I was low in order to

minimize potential side effects. Because IGF-I has been associated with development of certain type of tumors such as colorectal, breast and prostate cancers [21–23], we excluded patients with higher oncogenic risk such as cirrhosis of viral origin, hemochromatosis and individuals with α-fetoprotein $>10$ μg/l. We also attempted to minimize the influence of other disorders (such as diabetes, active alcohol ingestion, bleeding) that might confound the interpretation of the results. These exacting selection criteria contributed to the small number of subjects enrolled in the trial and this constitutes a limitation of the study. Also, because of the low IGF-I dose used the goal of hormonal replacement was not achieved, as serum IGF-I levels remained below normal values in the treated patients. Despite these limitations our study showed two main findings in IGF-I-treated patients: (a) a significant increase in serum albumin which correlated positively with the IGF-I/IGFBP-3 ratio, and (2) a trend toward improvement in REE which reached significance in the subgroup of alcoholic cirrhosis. Alcoholic cirrhosis and PBC differ with respect their pathogenetic mechanisms being the former an example of parenchymal liver damage and the latter the paradigm of cholestatic hepatic injury. In our study, the beneficial biological effects of IGF-I appeared to be more prominent in the subgroup of patients with alcoholic cirrhosis. However, whether the effect of IGF-I supplementation is different depending on the etiology of cirrhosis requires further studies.

Our data suggest that IGF-I may exert in cirrhotic patients a local effect on the liver, manifested as an improvement of albumin biosynthesis, and also a systemic metabolic action leading to increased energy consumption. Both findings are consistent with pre-clinical observations in cirrhotic rats where IGF-I improved liver function and nutritional status [11,12,15]. It has been proposed that IGF-I may act as a hepatoprotective factor by lessening oxidative liver damage, by decreasing the expression of pro-inflammatory molecules in the liver and by inducing other hepatoprotective substances such as hepatocyte growth factor (HGF) [15, 24]. In addition, the effects of IGF-I outside the liver, such as on intestinal function [11,12], on gonads [14], and on intermediate metabolism [11], may contribute to clinical improvement. Our finding that IGF-I therapy tends to increase REE is consistent with the anabolic action of this hormone, since it has been reported that REE decreases with the progress of liver cirrhosis [25], possibly as a reflection of reduced lean body mass. Although the mechanism by which IGF-I influences REE in cirrhotic patients remains to be clarified, in healthy subjects IGF-I has been shown to increase REE by modulation of substrate oxidation [26].

Our findings show that patients with liver cirrhosis tolerate IGF-I well, without significant side effects. Although increased IGF-I levels have been related to the development of certain types of tumors [21–23], a recent report [27] has shown that the case may be the opposite with respect hepatocellular carcinoma (HCC). These authors showed that the risk of HCC development increased when IGF-I dropped below a critical level during the evolution of liver cirrhosis [27]. With regard the risk of cancer, it should be noted that we attempted to perform replacement therapy and not to induce pharmacological effects associated with serum values above normal range. In our study we have not observed occurrence of liver nodules, nor elevation of alpha-fetoprotein in IGF-I treated patients. However, this preliminary observation would need to be confirmed in larger trials involving a higher number of patients with cirrhosis of diverse etiology.

In our trial levels of total IGF-I concentration at the end of therapy increased but did not reach normal age-adjusted values in the majority of treated patients. This might be due to the relatively low dose used and also to the fact that IGF-I was given only once daily and blood sampling was performed 24 h after the last IGF-I dose. Since in normal individuals half-life of this hormone is about 15 h [28] and might be shorter in cirrhotics due to decreased IGFBP-3 [8], the circulating levels of IGF-I in our trial could be below normal values part of the day. Future studies should define IGF-I pharmacokinetics in liver cirrhosis to allow adjusting the dose and the timing of IGF-I administration to the specific needs of these patients in order to optimize the therapeutic benefit. It should also be mentioned that we found no differences in free IFG-I between groups at the end of the study. Dissociation between the increase in total and free IGF-I has been observed in other conditions, such as the treatment of hypothyroidism that increases total IGF-I while free IGF-I remains unchanged [29]. This may be related to complexities in the regulation of the IGFBP system that involves at least six different proteins influencing free IGF-I concentration.

In conclusion, despite the limitations of this study our findings indicate that low doses of IGF-I given once daily for 4 months is well tolerated in liver cirrhosis. The observed improvement in albumin and REE may be consistent with a clinical benefit in cirrhotic patients. These preliminary findings warrant further study in larger clinical trials.

## 9. Conflict of interest

B. Scharschmidt is Vice President of Chiron Corp. and C Yoshizawa is Director of Biostatistics of Chiron Corp. The rest of the authors have no conflict of interest.

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