

POINT OF VIEW

Insulin-like growth factor I (IGF-I) and liver cirrhosis

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RESUMEN

El factor de crecimiento semejante a la insulina tipo I (IGF-I) es una hormona polipeptídica segregada en múltiples tejidos por efecto de la hormona de crecimiento (GH). Es responsable de parte de las acciones de la GH y además tiene efecto hipoglucemiante y anabolizante. El 90% del IGF-I circulante es de origen hepático y ejerce efectos autocrinos, paracrinos y endocrinos, estos últimos en múltiples tejidos. En la cirrosis hepática se produce una disminución progresiva de la producción hepática de IGF-I que llega a ser indetectable en la enfermedad avanzada. Algunas de las complicaciones de la cirrosis, fundamentalmente nutricionales y metabólicas (resistencia a insulina, desnutrición, osteopenia, hipogonadismo, alteraciones intestinales) podrían estar, al menos en parte, relacionadas con esta carencia de IGF-I dado que algunas acciones de IGF-I representan la imagen inversa de las complicaciones de la cirrosis. A pesar de ello, nunca se había propuesto tratamiento sustitutivo con IGF-I en la cirrosis. En una serie de estudios experimentales realizados en ratas cirróticas se demostró que el tratamiento con dosis bajas de IGF-I recombinante produce dos tipos de efectos en la cirrosis experimental: a) mejoría del hígado, dado que mejora la función hepatocelular, la hipertensión portal y la fibrosis hepática; y b) mejoría de las alteraciones extrahepáticas de la cirrosis dado que mejora la eficiencia del alimento ingerido, la masa muscular, la masa ósea, la función y estructura gonadales y la función y estructura intestinales con normalización de la malabsorción de azúcares y aminoácidos y la mejoría de la función intestinal de barrera manifestada por disminución de la endotoxemia y la translocación bacteriana. Posteriormente el primer ensayo clínico piloto, aleatorizado, doble ciego y controlado con placebo llevado a cabo en un número reducido de pacientes cirróticos demostró aumento de la albúmina sérica y mejoría del metabolismo energético por efecto del IGF-I. Se precisan ensayos clínicos adicionales para identificar la dosis adecuada de IGF-I, el tiempo y ritmo de administración y el subgrupo de pacientes cirróticos que obtendrán mayor beneficio de este tratamiento sustitutivo.

Palabras clave: Cirrosis. IGF-I.

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ABSTRACT

Insulin-like growth factor I (IGF-I) is a polypeptide hormone secreted by multiple tissues in response to growth hormone (GH). It is partly responsible for GH activity, and also has glucose-lowering and anabolizing effects. Ninety percent of circulating IGF-I originates in the liver and has autocrine, paracrine, and endocrine effects, the latter on multiple tissues. Liver cirrhosis results in a progressive decline of hepatic IGF-I output, and this factor may become undetectable in advanced disease. Some cirrhosis complications, mainly those nutritional and metabolic in nature (insulin resistance, malnutrition, osteopenia, hypogonadism, intestinal disorders), may be at least partly related to this IGF-I deficiency, since some IGF-I effects represent a reverse image of cirrhosis complications. Despite this, IGF-I replacement therapy has been never suggested for cirrhosis. A number of experimental studies in cirrhotic rats showed that therapy using low-dose recombinant IGF-I exerts two types of effect on experimental cirrhosis: a) liver improvement driven by improved hepatocellular function, portal hypertension, and liver fibrosis; and b) cirrhosis-related extrahepatic disorder improvement driven by improved food efficiency, muscle mass, bone mass, gonadal function and structure, and intestinal function and structure, with a normalization of sugar and amino acid malabsorption, and improved intestinal barrier function, manifested by reduced endotoxemia and bacterial translocation. Subsequently, the first randomized, double-blind, placebo-controlled, pilot clinical trial in a small number of cirrhotic patients showed increased serum albumin and improved energy metabolism as a result of IGF-I use. Further clinical trials are needed to identify adequate IGF-I doses, administration duration and frequency, and the subgroup of cirrhotic patients who will benefit most from this replacement therapy.

Key words: Cirrhosis. IGF-I.

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INTRODUCTION

Cirrhosis is a chronic, diffuse, irreversible liver disease characterized by the presence of necrosis, fibrosis, and regeneration nodules, which change the organ's structure and reduce the liver's functional mass. It is the final stage of a wide number of chronic liver conditions. All cirrhosis-related clinical manifestations ultimately depend on two factors: hepatocellular insufficiency from progressive hepatocellular mass reduction, and portal hypertension initially due increased intrahepatic resistance to portal flow, which results from distorted liver architecture.

For varying periods of time (years) cirrhosis remains in a "compensated" status, a term applied to patients who develop no serious complications. Complications arise in advanced stages, determine a poorer quality of life, and ultimately lead to the patient's demise ("decompensated" cirrhosis).

Most common complications of advanced cirrhosis include jaundice and coagulopathy from hepatocellular insufficiency, gastrointestinal bleeding from esophageal varices, ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, liver-related encephalopathy, and malnutrition (1,2). Survival in patients with compensated cirrhosis is relatively high. At 5 years after diagnosis 90% of patients remain alive (3), and at 10 years 50%, with a survival median of 15 years (4). However, should a complication develop, survival significantly decreases to 30% at 3 years (4). While in the past 20 years drug therapies have been developed that partly prevent or control some serious complications, none of them managed to significantly increase survival in these patients by modifying the disorder's natural history, except for etiologic therapies. Presently, liver transplantation is the only effective measure to improve the life prognosis of advanced disease. Therefore, new therapies are needed to modify the natural history of this disease, and to avoid or delay transplantation, so that the latter may be performed under better conditions. These therapies should improve hepatocellular function and reduce portal pressure through anti-inflammatory, anti-fibrogenic, anti-apoptotic, and regenerative mechanisms.

INSULIN-LIKE GROWTH FACTOR (IGF-I)

IGF-I is a polypeptide with endocrine, paracrine, and autocrine effects whose structure is 50% like that of insulin (5). Although many tissues secrete it, more than 90% of circulating IGF-I is synthesized in the liver (6).

Its output is stimulated by growth hormone (GH) (7), which is secreted by somatotrophic cells in the anterior pituitary. Liver cells have GH receptors that upon stimulation by the hormone increase IGF-I gene transcription (8); once synthesized IGF-I is released into plasma. IGF-I inhibits GH secretion both directly, by acting on the pituitary,

and indirectly, by stimulating somatostatin secretion in the hypothalamus, which in turn inhibits GH release (9). Thus a negative feedback circuit is established.

IGF-I circulates in the blood bound to proteins (IGF-BP), and interacts with specific receptors in target organs such as the muscle, bone, intestine, and testicles, among others (6).

At least seven binding proteins have been identified for IGF-I (IGFBPs) (10,11). These play a very important role in circulating IGF-I bioavailability, and their synthesis is under metabolic and hormonal control. Their functions may be summarized as follows (8): a) they serve as protein transporters in the plasma and control the flow of IGF-I from the vascular space to tissues; b) they prolong IGF-I half-life and regulate its metabolic clearance; c) they provide a specific localization tool; and d) they directly modulate the interaction between IGF-I and its receptor, and thus indirectly control IGF-I biologic activity.

In addition, at least some IGFBPs may directly exert biological effects outside IGF-I signaling pathways (12,13) including apoptosis induction and cell proliferation inhibition in some tumors, the latter being the case for IGFBP3.

Hepatocytes represent the greatest IGFBP1 and IGFBP3 source (9), but Kupffer cells also release IGFBP3 (14).

IGFBP3, by forming a stable ternary complex with an acid-labile subunit (ALS) and IGF-I, binds more than 95% of circulating IGF-I, and its production, as that of ALS, depends on GH and IGF-I (15). The ternary complex increases IGF-I half-life up to 15-20 hours (16), and thus keeps an IGF-I pool in the vascular compartment. Following the cleavage of this ternary complex by a protease IGF-I is released, and may then leave the circulation and enter target tissues with the help of other IGFBPs (5).

IGF-I acts in tissues by binding a specific receptor on cell membranes. This receptor is very similar to that of insulin. It is a α_2 , β_2 -heterotetramer. Alpha subunits are extracellular domains with cysteine-rich regions, which confer specificity to ligands. Beta subunits are cytoplasmic domains where tyrosine-kinase activity resides. Tyrosine phosphorylation activates a signaling cascade (17). IGF-I receptors preferentially bind IGF-I, but also IGF-II and insulin. IGF-I may also interact with other receptors, including insulin and IGF-II receptors, but with a much lower affinity (8). Whereas insulin has endocrine effects predominantly on the liver, fat tissue, and muscle, IGF-I has paracrine, endocrine, and autocrine effects on nearly all organs, including the immune system (9).

Serum IGF-I concentrations depend on GH secretion, age, gender, and nutritional status (5,18-20).

The relevance of IGF-I for fetal development and during childhood and adolescence has been known for years, as it is the primary factor responsible for many GH effects. The most significant expression of IGF-I deficiency is Laron-type dwarfism. In this condition an absence of GH receptors blocks IGF-I production. Early detection

allows to effectively treat these patients by administering exogenous rhIGF-I (21,22).

An important role of IGF-I for multiple adult organs has gained recognition during the past few years. Some of the reported effects are discussed below.

Essentially, IGF-I is an anabolic or growth factor. In protein metabolism it reduces proteolysis and stimulates protein synthesis when amino acids on offer are adequate (23). In the muscle it increases muscle mass (24). GH increases amino acid uptake by the muscle through an –at least partly– non-IGF-I-mediated effect (25), and thus effects by both substances are synergistic for increased muscle mass. IGF-I increases glucose use by stimulating its peripheral uptake, and inhibits liver glucose output (5). It has therefore an antidiabetic or glucose-lowering effect similar to insulin. In this respect its action is opposed to that of GH, which promotes hyperglycemia. This IGF-I effect probably aims at countering GH activity on carbohydrate metabolism, and maintaining euglycemia. In the presence of insulin resistance, besides its stimulation of glucose use by peripheral tissues, IGF-I reduces insulin resistance and insulin secretion by acting upon beta-cells in the pancreas (5). IGF-I also inhibits glucagon secretion (26). The effect of IGF-I on fat metabolism is weak. In the bone IGF-I increases the synthesis of collagen by facilitating l-proline transport and incorporation (27), and thus contributes to bone mass maintenance. It has trophic effects on the testicle (28), and has a trend towards increasing testosterone production, which in turn may help increase bone and muscle mass. In addition, it seemingly has trophic effects on the bowel, since both the bowel's length and mass are increased in transgenic mice with IGF-I overexpression, as are jejunal villi height and crypt depth (29). A trophic effect on the central nervous system has also been reported, which results in increases neuronal growth, brain size, and cortex surface in transgenic mice with IGF-I overexpression in the brain (30).

GH-IGF-I SYSTEM CHANGES IN CIRRHOTIC PATIENTS

Liver cirrhosis is a condition with IGF-I deficiency, which becomes more severe with disease progression, according to all reported studies (31-35). IGF-I levels are reduced in cirrhotic patients, whereas GH levels are increased (36). IGF-I deficiency results from two factors: a decrease in GH receptors seen in cirrhotic livers (37-39) and a progressive reduction of liver synthesis capability from decreased hepatocellular mass in advanced stages. Increased GH is accounted for by a lack of negative feedback on its secretion when plasma IGF-I declines. The liver's unresponsiveness to GH has been revealed by the infusion of exogenous GH in cirrhotic patients with advanced disease (Child-Pugh C), which only increases IGF-I by 10%, while the result is 20% in healthy subjects

with far higher baseline IGF-I levels (34). IGFBPs are also modified in cirrhosis, with particularly increased IGFBP1 and decreased IGFBP3 levels, which may alter this hormone's bioavailability in tissues (35,40,41).

According to the above, some characteristics of intermediary metabolism and malnutrition in cirrhosis may be partly justified by IGF-I deficiency. In fact, cirrhotic patients with malnutrition exhibit characteristics similar to those of prolonged fasting. Glucose production through liver gluconeogenesis is increased, as is proteolysis in the muscle. However, in contrast to healthy fasting subjects, cirrhotic individuals have increased insulin and glucose levels, which is typical of insulin resistance. The genesis of such insulin resistance is not well known. Suggested causes include high GH, glucagon, and catecholamine levels, and IGF-I deficiency (42). However, later studies suggested that neither GH nor glucagon exert a determinant influence over insulin resistance in cirrhotic patients (40). Schmueller et al. (40) suggest a relevant role for IGFBP1 in modulating insulin responsiveness. High IGFBP1 and decreased IGFBP3 levels may restrict IGF-I bioavailability and, as a consequence, insulin resistance as seen in cirrhotic subjects may result from reduced IGF-I bioavailability.

Low IGF-I levels have also been shown to play a role in the loss of bone mass displayed by cirrhotic individuals (43).

Despite the fact that cirrhosis is a specific hormone deficiency (IGF-I) no replacement therapy has ever been approached with the administration of exogenous IGF-I in this disease. This fact is in contrast with the clinical rule of treating hormone deficiencies with exogenous hormones when available. There is consensus that hypothyroidism, adrenal insufficiency, and diabetes should be treated with thyroid hormone, glucocorticoids, and insulin, respectively. The hypothesis that IGF-I deficiency may play a physiological role in the genesis of some cirrhosis complications led to suggest experimental studies to test it. Experimental data supporting the use of IGF-I as hormone replacement therapy in cirrhosis are discussed below.

EFFECTS OF rhIGF-I ADMINISTRATION IN EXPERIMENTAL CIRRHOSIS

Highly encouraging results in cirrhotic rats treated with rhIGF-I *versus* placebo have been reported. Following the subcutaneous administration of low-dose rhIGF-I (20 µg/kg/day) in short courses (14 or 21 days) to rats with carbon tetrachloride- and phenobarbital-induced cirrhosis we observed the following effects:

1. Increased food ingestion, increased efficiency regarding ingested food use, increased uptake of dietary nitrogen by muscle, and increased nitrogen balance (44), with a resulting increase in muscle mass. All quoted variables were altered in cirrhotic rats when compared to control rats.

2. A normalization of galactose intestinal absorption, and recovery of cirrhosis-associated villi atrophy (45-47). It should be highlighted that untreated cirrhotic animals have severe morphologic changes in their intestinal microvilli, and marked galactose malabsorption. These findings have been seen both *in vivo* (46) and *in vitro* (45). The fact that functional absorption changes parallel the structural recovery of intestinal mucosa suggests that the trophic effect of IGF-I on the mucosa is crucial for absorption's return to normal. This effect on jejunal microvilli has been reported both in early and advanced cirrhosis, with a normalization of microvilli atrophy following the administration of rhIGF-I (47).

3. A normalization of intestinal absorption for 4 distinct amino acids in studies of vesicles taken from intestinal mucosal brush borders from both treated and untreated rats (47,48). As in the above-mentioned galactose absorption studies, functional changes improve in parallel with morphologic changes. However, moderate lipid malabsorption as exhibited by cirrhotic animals does not improve (49).

4. Osteopenia improvement. An increase in bone density without changes in bone biochemical structure was reported. This effect results, at least partly, from reduced bone resorption (50,51).

5. A reversion of testicular atrophy and testicular histological changes occurring in cirrhosis, including loss of the blood-testicle barrier, decreased tubule diameter, germ line loss, and reduced cell proliferation and spermatogenesis both in early (52) and advanced disease (53). There is an additional trend towards the normalization of pituitary-gonadal axis function (53).

6. A restoration of somatotropic tone, which is reduced in cirrhosis and facilitates the inhibition of GH secretion (54).

7. Reduced portal pressure, endotoxemia, and bacterial translocation (55). We highlight the fact that no superposition of portal pressure values occurred between cirrhotic rats treated and untreated with IGF-I. Improved endotoxemia and bacterial translocation likely reflect an improved intestinal barrier function preventing intraluminal contents leakage. This improvement was seen in association with reduced THF- α expression and increased COX-2 expression in enterocytes by IGF-I. Decreased portal pressure probably reflects liver histology improvement with reduced fibrosis, but changes in non-structural aspects cannot be excluded.

8. Improved liver function, regarding both synthesis (increased albumin and coagulation factor levels) and transport (reduced bilirubin), and decreased liver fibrosis (decreased collagen in liver tissue and improved histological fibrosis score) (56). These findings are striking, as healthy liver hepatocytes have a low expression of IGF-I receptors (57), and hence no effect of exogenous IGF-I on liver tissue could be expected. However, no marked IGF-I receptor expression has been seen in regenerating hepatocytes, also in cirrhosis, which could explain this

effects (58). The intimate mechanism for these actions is unknown in its details. Following therapy with rhIGF-I cirrhotic rats exhibit a normal mitochondrial function in the liver (56), a decrease in oxidative stress parameters and enzymes MPO and iNOS –highly elevated in this type of carbon tetrachloride-induced cirrhosis– (59) and an increase in antioxidating enzymes such as SOD, catalase, and GSHPx (56). From these findings it may be concluded that IGF-I reduces lipid peroxidation and increases antioxidating activity in the cirrhotic liver, thus protecting the liver from carbon tetrachloride-induced damage. In addition, peroxidation products and free radicals can stimulate collagen gene expression in myofibroblasts (60), and prolyl-hydroxylase (61) (the enzyme on which collagen synthesis depends) activity, and activate stellate cells (62). All these changes regress following the administration of low-dose rhIGF-I, which demonstrates IGF-I's antifibrogenic effects (63). An interesting study (64) demonstrates that transgenic mice producing IGF-I under α SMA (α -smooth muscle actin, expressed in stellate cells in the liver) promoter control experience a reversion of their carbon tetrachloride-induced tissue damage, and have their transaminase levels reduced. These effects are seemingly mediated –at least partly– by the activation of HGF (hepatocyte growth factor, which stimulates tissue regeneration) and inhibition of TGF β 1 (stellate cell activator, hepatocyte proliferation inhibitor, and fibrogenesis promoter).

Several genes have been identified whose expression is altered in carbon tetrachloride-induced cirrhosis. Treatment with rhIGF-I normalizes expression in half of them (65). One is serpine 2, a serine-protease inhibitor that is considered the most relevant protector of mitochondria. In addition, rhIGF-I increases regenerating activity, thus increasing proliferating cell nuclear antigen (PCNA) expression, and partly restores GH receptor gene expression. It has been also reported to stimulate hepatocyte growth factor production, this factor being a potent mitogen and liver-protecting agent (66).

Studies performed by another team have demonstrated the liver-protecting effects of IGF-I in rats with experimental cirrhosis induced by common bile duct ligation. Animals receiving rhIGF-I had their liver function parameters improved, oxidative damage decreased, and fibrosis extent reduced in histological studies (67).

Furthermore, by euglycemic clamping cirrhotic rats using IGF-I increased glycogen synthesis in muscle tissue and reduced endogenous glucose output were reported, which thus improved insulin resistance (42).

Such liver-protective effects of IGF-I may contribute to improvements seen in liver function and liver fibrosis.

Overall, then, the administration of low-dose exogenous rhIGF-I to cirrhotic rats improves:

1. The cirrhotic liver, given improvements seen in liver fibrosis, hepatocellular function, and portal hypertension. Increased hepatocellular function and lessened portal hypertension are capital facts from a clinical standpoint, as

they are determinant of cirrhosis-related clinical manifestations.

2. Cirrhosis-related extrahepatic complications: nutritional status, osteopenia, sugar and amino acid absorption, intestinal barrier function, and gonadal function and structure. This improvement probably depends on both IGF-I's direct effects on target organs and improved hepatocellular function.

IGF-I ADMINISTRATION TO NORMAL SUBJECTS

The actions of IGF-I on metabolism, cardiovascular function, and renal function were assessed in healthy subjects. Most of these studies involved acute, variable-dose rhIGF-I administration through the intravenous route in continual infusion for 2- to 8-hour periods, or through the subcutaneous route for 4-week periods at most. In both cases wide dose ranges were used.

Metabolic effects are dependent on, and to a great extent similar to those of insulin.

The following tables summarize rhIGF-I effects following its administration to healthy subjects:

Table I

<i>Function</i>	<i>rhIGF-I effects</i>
Glucose metabolism	↑ glucose uptake ↓ liver glucose output ↑ insulin responsiveness Hypoglycemia (particularly when IV)
Lipid metabolism	↓ ketones, ↓ triglycerides, ↓ FFA
Protein metabolism	↑ protein synthesis ↓ nitrogen excretion ↑ muscle mass Improved healing
Renal function	↑ glomerular filtration, ↑ renal plasma flow
Counterregulating hormones	↑ catecholamines ↓ GH, ↓ glucagon

rhIGF-I ADMINISTRATION TO HUMANS UNDER PATHOLOGIC CONDITIONS

rhIGF-I is a therapeutic agent because of its wide variety of biological actions on various tissues. As a result of all such effects it has been posited a therapy against osteoporosis (68,69), catabolic situations such as burns (70), diabetes (71,72), obesity, neuromuscular disorders (73,74), GH resistance, and insulin resistance. Overall, it may be concluded that rhIGF-I has a glucose-lowering effect by diminishing peripheral insulin resistance, which favors diabetes control, increases protein synthesis, induces urinary nitrogen retention, augments bone and muscle mass, en-

hances muscle strength, and decreases both catabolism and fat mass. rhIGF-I was used in doses of 15 and 320 µg/kg/day through the subcutaneous route, and tolerability was excellent for doses below 80 µg/kg/day. Doses of 160 and 320 µg/kg/day were associated with edema, temporomandibular joint complaints, headache, dyspnea, tachycardia, weight gain, gynecomastia, avascular necrosis, Bell's paralysis, increased intracranial pressure, and occasional hypoglycemia episodes.

When IGF-I levels are very low (Laron-type dwarfism) therapeutic effects become much more intense and side effects are nil, which is consistent with the actions expected from a hormonal replacement therapy, where a physiologic rather than pharmacologic effect is sought.

IGF-I AND CANCER

A theoretical problem regarding IGF-I administration in cirrhosis is the potential risk of administering a growth factor is a pre-neoplastic condition such as cirrhosis.

Literature reports suggest a potential role of endogenous IGF-I in tumor growth, but no definite data are available in this respect (75). Major data are as follows:

1. An epidemiologic study attempted to establish a relationship between serum IGF-I levels and prostate cancer (76). Patients whose IGF-I plasma concentrations fell within the fourth quartile (294-500 ng/ml) had a relative risk of prostate cancer that was 2.41-fold higher than that of subjects with IGF-I levels in the first quartile (99-185 ng/ml). Other studies have confirmed this, but no causal relationship could be established (77).

2. Patients with acromegaly, who are exposed to high plasma growth hormone, IGF-I, and insulin levels for years, have an increased risk of colon adenocarcinoma (78).

3. A positive correlation has been seen between plasma IGF-I levels and breast cancer risk in premenopausal but not postmenopausal women. No association was found between IGF-I concentrations and cancer risk across patients (79). IGF-I is also considered an activity marker for this type of tumor (80).

4. Epidemiologic studies have suggested that high IGF-I levels are associated with increased risk for colorectal, lung, and prostate cancer when compared to healthy subjects with lower IGF-I levels (81).

5. Many tumor cell lines have IGF-I receptors, produce IGF-I, and respond to IGF-I administration (82).

6. Inhibition of IGF-I-receptor binding using antibodies blocks tumor cell growth in thymusless mice. Glioblastoma development in rats may be prevented or treated using immunogenic C6 cells expressing antisense IGF-I mRNA (83).

7. No data in the literature suggest the malignant transformation of a normal cell in association with IGF-I administration.

8. No tumor development has been reported in patients receiving IGF-I to this day.

9. IGF- I has not been associated with hepatocarcinoma development.

While these studies establish no cause-effect relationship between IGF-I levels and tumor development, it is only logical that therapies using this hormone have a replacement purpose, never elevating IGF-I levels above upper normal limits in a sustained manner.

rhIGF-1 ADMINISTRATION TO PATIENTS WITH CIRRHOSIS

Only one clinical trial has been performed thus far where hIGF-I was chronically administered to cirrhotic patients (84). It was a pilot, double-blind, randomized, placebo-controlled study to assess the effects of rhIGF-I administration to patients with alcohol-related cirrhosis or primary biliary cirrhosis for four months. Initial doses of 20 mg/kg/day followed by weekly increases were administered to reach a maximum of 50 µg/kg/day or 100 µg/kg/day after four weeks.

The goal of the study was to administer replacement therapy by giving in an exogenous manner what patients could not synthesize. To be included patients had to exhibit very low IGF-I levels (lower than mean IGF-I –2 SDs).

Eight patients with alcoholic cirrhosis and one with PBC received rhIGF-1, and seven patients with alcoholic cirrhosis and two with PBC received placebo.

The study goals included an assessment of rhIGF-I effects on the IGF-I/IGFBP system, liver function, and nutritional status.

When critically assessed this study has two major limitations: a low number of subjects, as this was a pilot study, and IGF-I doses that failed to fully meet replacement goals, as patients did not achieve normal IGF-I values over the study period.

The study showed three main findings in patients receiving rhIGF-I:

1. A significant increase in serum albumin levels that correlates to IGF-I/IGFBP3 ratio, an index of IGF-I bioavailability.

2. A trend towards increased resting energy expenditure (REE) that reaches significance in the alcoholic patient subgroup.

3. Total IGF-I and IGF-I/IGFBP3 ratio levels rose among patients receiving rhIGF-1, although IGF-I concentration reached normal values at 7 hours after injection, only to fall back below normal limits at 24 hours.

IGF-I was more effective in patients with less nutritional impairment, higher hormone bioavailability rates, and alcoholic cirrhosis.

Another interesting finding was an excellent tolerability with no major side effects ever reported.

FINAL CONSIDERATIONS

Insulin-like growth factor I (IGF-I) may be considered an early marker of functional reserve or hepatocellular functional capacity (85,86). A marked decline is seen in early cirrhosis stages (Child-Pugh A). It is already elevated before other liver function involvement parameters (decreased albumin, prolonged prothrombin time, hyperbilirubinemia) increase (85). In addition, several studies have shown that, following the administration of GH to cirrhotic patients, a greater synthesis of IGF-I screens patients bound to have better survival (87). A marked decline of IGF-I has also been described of being associated with a higher probability of hepatocarcinoma (88) and poorer prognosis in patients requiring liver surgery (89). As a result IGF-I levels are considered of prognostic value regarding survival in cirrhotic patients (85,90,91).

IGF-I levels are likely to ultimately result from many synergistic factors. Primary amongst them is liver disease severity, with its ensuing loss of hepatocytes and non-parenchymal liver cells, the ones who can secrete IGF-I and its binding proteins. Other factors influencing IGF-I levels include nutritional status (92), portal hypertension extent, and hyperestrogenism, all of them partly associated with liver disease development (85).

The association of the liver's functional stage (Child-Pugh) with the measurement of IGF-I and IGFBP3 levels, both baseline and following stimulation with GH (87), predicts disease severity more accurately than Child-Pugh staging alone (93).

While liver transplantation is the only effective therapy for cirrhosis, it is important that adjuvant treatments leading to prolonged survival –either from disease and complication improvement or from making it to transplantation in a condition as good as possible– be investigated.

The above-mentioned results render further studies necessary to confirm benefits thus far reported. Furthermore, studies should attempt to establish doses, dosage frequency, and treatment duration with IGF-I. Whether beneficial effects are influenced by cirrhosis etiology or disease stage should be investigated in order to identify patient subgroups most likely to benefit from this therapy. These studies represent a first step towards cirrhosis therapies beyond complication prevention or treatment, therapies that may modify the natural history of this disease and hence delay or ideally cancel liver transplantation.

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