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Research Article

Security and Efficacy of Intra-Portal Infusion of Autologous Stem Cells for Liver Regeneration a Randomized Pilot Study

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Abstract

Aim: To analyze security of intraportal infusion of autologous stem cells during portal embolization to increase remanent liver volume.

Methods: Phase II clinical trial studying intraportal infusion of autologous stem cells processed from patient bone marrow. Stem cells are applicated during preoperatoy portal embolization used to increase the volume of remanent liver in patient's subsidiary of major hepatectomy.

Results: 12 patients, of which 5 have undergone PE and intraportal infusion of SC: liver metastasis of colorectal carcinoma 40% / 42.8%, hepatocellular carcinoma 40% / cholangiocarcinoma 28.6% and 20% / 28.6%. Average bone marrow extracted in SC-group patients was 270 cc, having infused a mean of 36 cc of intraportal SC. Not fever cases, not portal vein thrombosis liver abscess or tumor disease progression were detected. Biopsies token during hepatectomy did not show fibrosis or hepatic steatosis different from ablated tissue. Differences in the increase of the volume of the remnant liver were not statistically significant.

Conclusion: The intraportal infusion of autologous stem cells, extracted and processed from the patient's own bone marrow, using the procedure portal embolization for intrahepatic infusion, appears to be a safe method.

Keywords: Stem cells; Portal embolization; Liver resection

Background

To date management of patients with liver tumors which required extended hepatectomy is performed by performing preoperative embolization segments in which the lesion is located, to facilitate regeneration of the remaining segments, which allows performing safer surgery. However, the response to the contra lateral embolization site is slow and often has an excessive time to tumor growth that occurs, thus precluding sometimes curative treatment. Recently, the treatment being investigated by implantation of adult progenitor cells derived from the bone marrow into the portal vein of the remaining segments with promising results cells. The application of adult stem cells in hepatic regeneration treatment is included as part of the regenerative medicine and is an advanced technique in this field.

Liver regeneration

At present it is considered that liver regeneration is a process that takes place in several phases, of which two are critical: a] the transition from quiescent hepatocytes [at rest] to enter the cell cycle and b] their progression through the G1 phase of the cell cycle. These steps are critical to the hepatocyte, as are the bridges between a proliferative and an apoptotic process [1-3].

Capacity of hepatocyte regeneration

After performing a partial hepatectomy (70%], liver regenerates once or twice by dividing hepatocytes to complete this process and return to their quiescent state [4]. Hepatocyte replication does not exceed more than two cycles; nevertheless retained their proliferative capacity. It has observed after regain its lost ground, if a new segment of the liver is removed; restart the hepatocyte cell cycle and doubles [2-4]. The ability of multiplication has clearly been demonstrated in transgenic mice deficient in grow factors. These animals are born with a genetic defect that prevents them from having a healthy adult liver, so they die early. These animals were transplanted hepatocytes proliferate healthy animals to restore proper mass and liver function. When liver recover their function, are used as donors to other transgenic animals and recovering the latter, like the first, the function of the transplanted hepatocytes. Such transplants have been tested up to eight rounds; in each case, the transplanted animals recover their function without apparent mass and decrease in proliferative capacity of hepatocytes [5-8]. It has also been found that in serial transplantation, where using the same parent cell line, cell populations 7 x 1020 more times than the original population (greater than the proliferative capacity of hematopoietic tissue Index) [5-8] is doubled.

The hepatocyte proliferative capacity is not associated to the size, location within the hepatic lobule or number of cores it has. Neither is associated with the proliferative capacity and age of the donor, as both young adults and the elderly have the same proliferative capacity of their hepatocyte. Such studies have indicated that the hepatocytes in normal state, have suppressed their proliferative capacity and that

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the agency maintains the regulation of cell proliferation to express at the right time [5-8].

Precursor cells in the liver

The proliferative capacity of adult hepatocytes explains the coexistence within the liver, precursor cells or stem cell [stem cell]. Found ductal liver epithelial cells and cells with ability to differentiate into hepatocytes, bile ducts [channels Herring]. These are a "cellular reservoir" in the adult liver, as they are able to differentiate into mature hepatocytes or ductal cells after acute intoxication, massive necrosis or any other damage to liver tissue. When liver damage occurs by any of these causes, the ductal cells are transformed into a specific type of indifferenciate cells, called "oval cells", which are grouped into "clusters" to form an "oval box" where performs the cell proliferation. If research demonstrating lack oval cells are the original progenitor maintained in steady state in the liver or constitutes the first pluripotential precursor previous to primitive cell [9-15].

The transcription factor NFkB [Nuclear Factor κ Chain in B Lymphocytes] and STAT3 are two of the major proteins that are activated at the start of liver regeneration. These do not require prior synthesis protein, since only depend on post-transcription mechanism activated [16-22]. The transcription factor STAT3 is activated more slowly than the NFkB and activation mechanism is completely different. After partial hepatectomy, STAT3 is activated in the first two hours and stays active for four to six. STAT3 is a member transcription factors known as "signal transducers and activators of transcription" [Signal Transduction and Activators of Transcription]. So far, seven members of this family, of which the best known STAT3 is known. Its activation by cytokines, such as interLeukin-6 [IL-6],using a specific receptor for the translation of intracellular signals [22-24]. This receptor binds two important growth factors for the liver, such as TGFa and Hepatocyte Growth Factor [HGF], so that they stimulate regeneration and healing of the liver. The activation and inhibition of gene expression is a complex process during the early stages of liver regeneration. It is important to know how to start the regenerative process and activation and inhibition of transcription factors regulate and maintain the initial activation process early genes, in addition to understanding their participation in each phase of the regeneration cycle. It is accepted that growth factors and cytokines are first molecular elements to initiate and to mark the hepatocyte proliferation. The main growth factors, identified as initiators of the regenerative process, comprising at TGFa, HGF, EGF and IL-6. These have been shown, separately or in combination, lead to a hepatocyte of the G0 state [quiescent state] to G1 [initial active state] of the cell cycle. Growth factors released in the initial process of hepatic regeneration, activated transcription factors early genes and for the cell through the quiescent cells to the G1 phase of the cell cycle. In addition, these factors promote cell progression through G1 phase and whether favorable conditions, passing the "critical control points" to duplicate its genetic material into the S phase of the cycle. Once the cell passes through the "hot spots" of the G1 phase, takes the total cell cycle into a "domino effect" where one active to another system to complete all phases of the cell cycle [25-28].

Portal embolization

Preoperative Portal Embolization [PE] emerged from the need to increase the number of candidates for surgery, especially in those patients in whom the future liver remnant would not ensure hepatocellular function. In the 1980s, in Japan, several studies led to the development of the PE; firstly, it began to be embolized, during surgery branches afferent hepatocarcinomas portals to avoid dissemination to healthy transportal territory. In the pre-intervention or in patients who, for various reasons, could not be operated period, a marked hypertrophy not embolized tissue was observed. It is also that in patients with liver tumors [cholangiocarcinoma type] with a progressive infiltration of portal vein, an increase in volume of sound produced known territory. These observations led to Makuuchi et al. Practice PE for growth the liver would not be resected.

Since then, many series, articles, papers and reviews presented in the literature on PE, and still remains controversy over the technical approach, the ideal embolization material, or on the indications and contraindications. The fundamental goal of PE is to induce hepatic atrophy tumor area with remnant liver hypertrophy. The aim is to increase the number of candidates for surgery, offering survival rates similar to those of patient groups in the preoperative staging was more favorable.

In addition, improving the hepatic functional reserve will be sought to decrease the possibility of encountering postoperative complications related mainly to liver failure. For reasons not yet well known, after hepatic aggression [partial surgical resection, portal vein occlusion] cellular mechanisms of liver regeneration are triggered. The hepatocyte has a great capacity for dedifferentiation [hepatocyte appearance of 'fetal type'] and clonal expansion. The primary responsibility of this role will be the hepatocyte growth factor [Hepatic Growth Factor [HGF]], other factors such as intrahepatic release Tissue Necrotic Factor [TNF], or extrahepatic release, such as insulin, act as comitogénicos with HGF. Another point to consider is that the embolized territory no cell necrosis will occur, therefore, no cytolysis [increased transaminases, pain, fever, etc.] but apoptosis, why is minimal postembolization syndrome after PE [29]. Remains debate over whether the embolic agent, whose choice will be discussed below, should produce periportal inflammation or no inflammation and that this, in addition to conditioning surgery may trigger mechanisms cellular necrosis [30].

Stem cells in liver regeneration

Hematopoietic Stem Cells [SC] derived from bone marrow are the most studied [31], especially since its discovery in the sixties as basic cells in the bone marrow hematopoiesis. Besides from bone marrow, the SC can also be obtained from peripheral blood and cord blood. The ease of obtaining these cells make them ideal for cellular therapies. Concerning liver regeneration, it has been found in several studies that the SC is able to activate the "hepatocyte-like cells" and repopulate the liver of mice by changing their phenotype [31-35]. The numerous studies published, it appears that the effectiveness of the isolated umbilical cord SC is greater than those obtained from peripheral blood or bone marrow. The mechanism by which the SC generates mature hepatocytes is still unknown. In some animal models occurs after the merger of these SC with host liver hepatocytes [36-39], although other studies SCs to differentiate into mature hepatocytes [40]. It is possible that the population of SC stimulate production of hepatocytes [41-43]. SC is not all equally effective. As

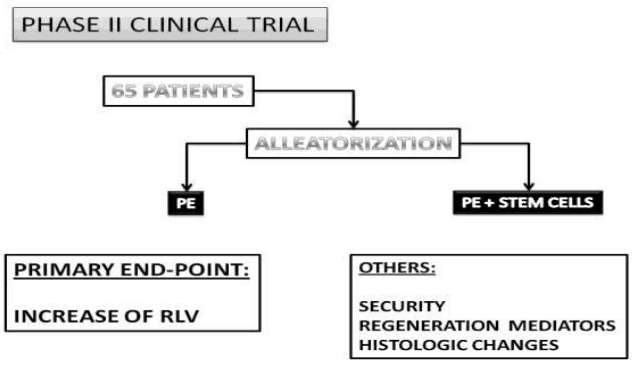

Figure 1: Phase II clinical trial scheme.
SC: Stem Cell; PE: Portal Embolization; RLV: Remanent Liver Volume

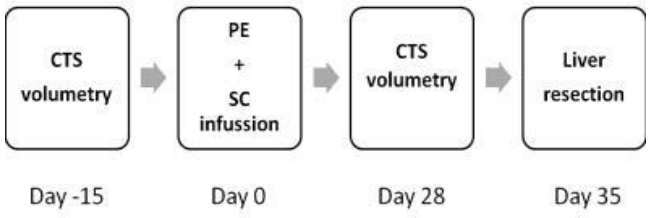

Figure 2: Phase II clinical trial chronogram.
SC: Stem Cell; PE: Portal Embolization; CTS: Computerized Tomography Scan

previously noted, the isolated peripheral blood are less effective. By contrast, the phenotype Lin-CD38 + BMCD34 seems to be the most stimulating liver regeneration [44, 45].

The use of the SC in liver regeneration of patients is still scarce. The problem is not only effective, but safe clinical administration is unknown. Studies have been published in various forms of administration of SC in patients undergoing hepatectomy and in cirrhotic patients [46-48]. There are no studies in which the SC is infusion of study prior to the completion of hepatectomy and evaluate their effectiveness by liver volumetric. Our study further characterized the SC are isolated from bone marrow of the patient, infusing via the portal site during preoperative PE.

Material and Methods

This article aims to issue the preliminary results of a phase II clinical trial, registered as EudraCT Number 2009-017793-20, to evaluate the efficacy of intraportal infusion of autologous stem cells extracted from the patient's own bone marrow, as co-adjuvant preoperative PE (Figures 1&2).

Study population

The study population corresponds to patients with hepatic space occupying lesion [LOE] that require an extended hepatic resection [more than four segments] and in the residual liver volume is insufficient to ensure liver function and the necessary safety margins after resection. Preoperative assessment of residual liver volume after hepatectomy is> 30% (> 40% in diseased livers). There are basically four types of liver lesions which are included in the study: extended right hepatectomy to segment IV, right hepatectomy with suspected diseased liver [esteatohepatitis secondary to neoadjuvant chemotherapy, liver fibrosis], hepatocellular carcinoma in cirrhotic liver subsidiary of right hepatectomy and liver benign lesions [hemangiomas, hydatid cysts or primary liver tumors which by extension threatening the viability of the remnant liver tissue.

Method of production of SC

The process for producing autologous bone marrow was performed in an operating room by repeated aspiration of the posterior iliac crest under local anesthesia and sedation until reaching a volume of approximately 500 ml of bone. The obtained marrow was collected in a transfer bag containing the ACD-A solution as an anticoagulant in a ratio of 1:5 of the volume of bone. The processing consisted of bone marrow plasma removal, red blood cells and granulocytes, obtaining only the SC. The procedure was performed by density gradient centrifugation on Ficoll-Hypaque density 1077 in an automatic processor SEPAX cells and SC suspension obtained was subjected to two washes with 4% human albumin in the same machine in order removing the Ficoll. After two washes, the cells were subjected to a final centrifugation to reduce the volume of the cell suspension, and finally resuspended in 10 to 30 ml of 0.9% NaCl. Once filtered through a 150µ filter, stored in sterile infusion bag. The final cell suspension distributed in the corresponding aliquots was transported in sterile conditions to the radiology suite for immediate administration to the patient.

Method for portal embolization

The puncture is performed using a 22 G Chiba needle with ultrasound guidance allowing proper localization of a portal vein. Once that punctured portal vein, which is confirmed by the introduction of contrast medium, a guide of 0.018 is introduced, later to exchange it for a guide of 0,035 more support through a system of rapid exchange. Subsequently, through the guidance of 0.035, an introducer is placed with valve 5F, initially having a pigtail catheter 5F, which is placed at the level of the main trunk of the portal vein, to practice portography and to assess properly the entire portal intrahepatic vasculature.

We proceed to selective catheterization of the right portal branches, using hydrophilic catheters Simons, Cobra and / or 5F vertebral type practiced selective phlebography back to pre-embolization assessment. When proper placement and catheter stability is confirmed we proceed to embolization, which is performed in two steps: 1. Microparticles of polyvinyl alcohol, in range of 150-300 / 300-500 microns, in order to obtain a distal embolization slowing of flow. 2 metal spirals [coils] of 0.018 or 0.035 with the embolization is complete. Finally, a control is performed portography, thrombosis obtained to confirm the right of portal vasculature.

Stem cells application procedure

After the embolization of the portal branches where the injury is located, proceed to the selective application of stem cells in the portal branches of the remaining liver segments. This application is made using a 5-F catheter cobra [Terumo] inserted in the branches of hepatic remaining segments under fluoroscopy. Following application of the cells intrahepatic, the portal catheter is withdrawn.

Results

So far we've included 12 patients, of which 5 have undergone PE and intraportal infusion of SC [SC group], and 7 patients underwent

Table 1: Patient's characteristics and Portal Embolization outcome.

Study Patients						Control Patients						
ID	SC-1	SC-2	SC-3	SC-4	SC-5	nonSC-1	nonSC-2	nonSC-3	nonSC-4	nonSC-5	nonSC-6	nonSC-7
Age	61	59	67	56	49	46	67	62	69	75	35	68
Gender	F	M	F	F	M	M	M	M	F	M	M	F
Primary disease	LM	HC	LM	CC	HC	LM	HC	CC	LM	LM	HC	CC
Embolized segments	04-Aug	01-Apr	05-Aug	05-Aug	05-Aug	05-Aug	05-Aug	01-Apr	05-Aug	05-Aug	05-Aug	05-Aug
Extracted BM (ml)	250	300	300	200	300							
Infused SC (m1)	50	40	40	20	30							
Get resection	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N
Resected segments	04-Aug	01-Apr	05-Aug	05-Aug	05-Aug	05-Aug	-	01-Apr	05-Aug	05-Aug	05-Aug	-

SC: Stem Cell; BM: Bone Marrow; PE: Portal Embolization; SC-group: Stem Cell group. NonSC-group: Non Stem Cell Group

Table 2: Patient's data for security of intraportal stem cell infusion.

Study Patients						Control Patients						
ID	SC-1	SC-2	SC-3	SC-4	SC-5	nonSC-1	nonSC-2	nonSC-3	nonSC-4	nonSC-5	nonSC-6	nonSC-7
Pain	No	No	Yes	No	No	No	No	No	Yes	No	No	No
Fever	No	No	No	No	No	No	Yes	No	No	No	No	no
Liver abscess	No	No	No	No	No	No	No	No	No	No	No	No
Portal thrombosis	No	No	No	No	No	No	No	No	No	No	No	No
Pulmonary embolism	No	No	No	No	No	No	No	No	No	No	No	No
Tumoral progression	No	No	No	No	No	No	No	No	No	No	No	No
Tumoral metastases	No	No	No	No	No	No	No	No	No	No	No	No
Hospital staying (d)	2	1	5	2	2	2	1	5	3	2	2	2

SC=Stem Cell.

embolization site without infusion of SC [nonSC group]. The phenotypic characteristics of patients can be observed in Table 1.

Both groups were comparable, with a mean age of 58.4 in SC group and 60.3 in nonSC group, and a similar distribution of underlying diseases: liver metastasis of colorectal carcinoma 40% / 42.8%, hepatocellular carcinoma 40% / cholangiocarcinoma 28.6% and 20% / 28.6%. All patients required PE prior to hepatic resection for a pathological liver tissue present: chronic hepatitis with fibrosis F2 [n = 3], cirrhosis [n=1], cholestatic hepatitis [n = 3], or toxic hepatitis by prior chemotherapy [n = 5]. The average bone marrow extracted in SC-group patients was 270 cc, having infused a mean of 36 cc of intraportal SC.

All patients in the SC group were able to undergo surgical resection [hepatectomy1 Left1 trisectorectomy, 3 right hepatectomy]. In two patients nonSC-group portal embolization failed and could not undergo hepatectomy, can undergo liver resection in 5 patients [1 Left hepatectomy, 4 right hepatectomies]. The reason for not resection of the two patients was Serratia infection liver leading to exitus of the patient and in the other patient, no improvement in liver volume.

The security of intraportal infusion of autologous SC extracted from the patient's own bone marrow can be seen in Table 2. Only one patient had right upper quadrant pain that prolonged hospital stay but not fever cases, not portal vein thrombosis liver abscess or tumor disease progression were detected.

Regarding the possibility that the SC may perform any remaining histological damage in the liver where they were infused, biopsies token during hepatectomy did not show fibrosis or hepatic steatosis different from ablated tissue.

Differences in the increase of the volume of the remnant liver were not statistically significant.

Discussion

Liver regeneration is the primary response against the liver tissue damage. It is a multifactorial process induced and controlled by specific stimuli both endogenous and exogenous that cause sequential changes in gene expression and the structure of the liver cells. Research in this field has increased considerably in recent years, which has allowed a better understanding of the process of organogenesis and possible clinical implications related. Our study is a phase II clinical trial, which provides significant clinical value.

This development has been based mainly on the development of animal models and has produced among other reasons because of the great interest in the possibility of its application to the clinic at different levels. Thus, many compounds have been proposed to enhance liver regeneration, most notably all growth factors. Within these, although the TGF [Transforming Growth Factor] that best correlates with plasma levels of DNA synthesis, is HGF [Hepatocyte Growth Factor] the considered the most potent growth factor [49], although no studies with growth factors have offered relevant clinical outcomes.

Most experimental studies of SC have been shown to be effective both *in vitro* and in experimental animals and, theoretically, your application could increase the chances of survival in the case of liver

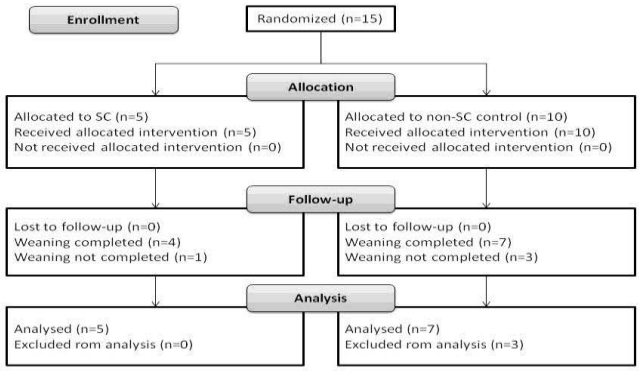

Figure 3: Phase II clinical trial enrollment and allocation.
SC: Stem Cell

transplants in cases of massive or acute injury induced hepatotoxic although there have been few studies to evaluate liver regeneration after hepatectomy performing. However, the lack of human studies has concluded that prevents real progress therapeutically. Other therapies also very promising, such as the administration of insulin and glucagon in liver regeneration after fulminant hepatic failure, it showed a significant role in experimental models and yet subsequent randomized trials showed that the combination these two hormones not provide beneficial effect in patients.

Parallel to the advancement of knowledge of the implementation of SC and growth factors by more or less conventional methods, have also been important advances in the knowledge of their application through gene therapy. In this therapy, genes are incorporated into appropriate vectors to facilitate entry and function within cells. A considerable number of preclinical studies are being conducted in this sense with very promising results; however one should be very cautious about this kind of technology, because sometimes your expectations have been exaggerated, regardless of who currently is an experimental technique.

Despite all the above drawbacks, the continuity of research in the field of SC is desirable and even required, since the range of possible therapeutic application in the field of hepatology is very attractive, including: 1 Resection of primary liver tumors; 2 Resection of liver metastases; 3 severe and fulminant acute viral or toxic origin hepatic failure: in this process, the process of massive necrosis is not compensated by the attempts of liver regeneration, which favored power, allow the return to normal liver parenchyma; 4 Facilitate recovery and success of transplantation, on all the "split liver".

Because of the very premature stages of development in which the experimental studies using SC in liver regeneration are found, the safety and efficacy data are still scarce. We cannot forget, however, that the safety analysis of a new intervention is always important, especially in situations like this, where it is even unknown whether therapeutic utility. The primary concern regarding the safety of the SC is able to play the role of administration on the development of tumors or to favor the progression of the underlying tumor disease if any. In this sense, and after 18 months of follow-up, we have not detected any tumor recurrence, disease progression or occurrence of new malignancies.

Some clinical studies have shown that exogenous administration of some growth factors extrahepatic caused adverse effects, mainly of renal origin [50]. In our study, renal function impairment did not suffer in any way. Locally, we have not objectified liver damage at the tissue level: we found no cases of liver abscess or trunk or peripheral portal trombosis.

There have been several studies in which SC was used marrow autologous animals and also in liver regeneration in cirrhotic patients. Most of these studies are not controlled. Infusion routes used are arterial or portal venous [51-54]. Some studies have used peripheral blood SC [55]. In our study, portal route has a zero incidence of complications, and has the advantage of the same procedure used during preoperative PE.

There are published several studies of SC in cirrhotic patients, showing an improvement in the levels of plasma bilirubin and in MELD and Child-Pugh scores [53-56]. Fewer studies have been reported regarding the use of SC prior to the completion of hepatectomy, and in any case, have always been infused peripherally, with more or less variable results. In our case, the use of intraportal provides an important patient safety, in addition to the same procedure used during the embolization site, which does not provide a new procedure for the patient. Although its effectiveness in increasing the volume of the remnant liver is seen when the number of patients is larger, we can say that the incidence of adverse effects is negligible.

Conclusion

The intraportal infusion of autologous stem cells, extracted and processed from the patient's own bone marrow, using the procedure portal embolization for intrahepatic infusion, appears to be a safe method that does not involve risk to the patient, beyond which could present embolization of portal itself. It may be an adjunctive method in the growth of liver segments prior to liver resection increased, but it is necessary to complete the clinical trial to see if patients undergoing intraportal infusion of SC have an increased growth of the remnant liver.

There have been many studies using autologous bone marrow SC infusion in patients to liver regeneration both in healthy or cirrotic organs. Optimization and randomized controlled testing of these protocols are needed, and once the mechanism of action is more fully understood, it is likely that new therapies suitable for use outside the tertiary referral center will emerge.

Author Contributions

Álamo JM and Padillo J coordinated the clinical trial, Carmona M and Herrera C performed the stem cell extraction; Peiró J performed the portal embolizations; Barrera L provided de collection of data; Muntané J provided vital reagents and analytical tools and were also involved in editing the manuscript; Bernal C, Marín LM, Suárez G, Serrano J and Gómez MA provided the collection and treatment of all the patients; Álamo JM designed the study and wrote the manuscript.

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