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TOPIC HIGHLIGHT

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Pharmacotherapy of acute alcoholic hepatitis in clinical practice

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Abstract

Severe alcoholic hepatitis (AH) is an acute form of alcohol induced liver disease with a poor prognosis that is seen in the patients who consume large quantities of alcohol. The diagnosis of AH is based on the appropriate alcohol intake history and is supported with clinical and histological features, and several scoring systems. Glucocorticoids are the mainstay for treating severe AH with pentoxifylline used as an alternative to steroids in addition to total alcohol abstinence. Liver transplantation is a possible therapeutic option for severe AH. Among the anti-craving medications able to improve abstinence rate, baclofen seems to be effective and safe in the alcoholic patients affected by severe liver damage.

Key words: Severe alcoholic hepatitis; Maddrey's discriminant function; Glucocorticoids; Baclofen; Orthotopic liver transplantation; Alcoholic liver disease

Core tip: The therapy of severe alcoholic hepatitis (AH) is a problem in clinical practice due to the complex of the pathogenetic mechanisms involved. However, several treatment options are now available. The specific treatment of AH is directed to acute injury in order to block the progression of the fibrosis. Orthotopic liver transplantation is a possible therapeutic option for severe AH in the non-responder patients. Baclofen seems to be effective and safe anti-craving drug able to improve abstinence in patients with severe AH.

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INTRODUCTION

Alcohol use disorders (AUD) is a major cause of preventable morbidity and mortality worldwide[1]. Severe alcoholic hepatitis (AH) is a serious form of alcohol-related liver injury that is seen in the patients who consume large quantities of alcohol during a prolonged period of time[2]. The term "acute alcoholic hepatitis" was first used by Beckett *et al*[3] in 1961 and included a spectrum of the severity ranging from the asymptomatic mild abnormalities of liver chemistry tests to the fulminant liver failure and even death. However, the term "acute" represents a rapid worsening of an underlying chronic liver disease, and severe AH is defined as an acute-on-chronic

liver failure in many patients. It remains important for the clinicians to detect and treat this complex disease competently and satisfactorily.

The risk of the alcoholic liver disease (ALD) increases with the dose and duration of alcohol consumption[4]. However, the history of this condition is also influenced by many host factors, in particular obesity[5], female gender[6], viral co-infection (*i.e.,* chronic hepatitis C infection)[7], and iron overload[8], that are well known to increase the risk significantly[9].

The acute ingestion of alcohol can cause several metabolic alterations, including hypoglycemia, lactic acidosis, hypokalemia, hypomagnesemia, hypoalbuminemia, hypocalcemia, and hypophosphatemia on different body parts and tracts[10,11]. Acute alcohol intoxication-related cardiovascular effects include tachycardia, peripheral vasodilation and volume depletion; these features can contribute to the induction of hypothermia and hypotension[12]. Another possible cardiovascular effect is the "holiday heart syndrome", characterized by atrial or ventricular tachyarrhythmias and a new onset of atrial fibrillation after the acute alcohol ingestion[13]. The main life-threatening respiratory consequence of acute alcohol intoxication is respiratory depression[14]. Other respiratory effects include decreased airway sensitivity to foreign bodies, decreased ciliary clearance and aspiration and increased risk of bacterial infection with consequent bronchitis and pneumonia. Gastrointestinal effects include nausea, vomiting, diarrhea, abdominal pain due to gastritis, peptic ulcer, and pancreatitis[15]. Prolonged vomiting can lead to hyponatremia. Acute alcohol intoxication can cause a dysfunction of esophageal, gastric, and duodenal motility and an increase in duodenal type III propulsive waves in the ileum; the increased transit of the intestinal contents may contribute to diarrhea[16]. Excessive alcohol consumption is also a risk factor for developing colorectal adenomas or colorectal cancer[17].

The symptoms are usually related to the blood alcohol concentration (BAC). At the BAC higher than 300 mg/dL (65.1 mmol/L), there is an increased risk of respiratory depression and arrest. The death attributable to acute alcohol intoxication generally occurs at the BAC higher than 500 mg/dL (108.5 mmol/L), although the lethal dose of alcohol can vary. Specifically, death was observed at lower BACs in the "non-tolerant" subjects (300 mg/dL; 65.1 mmol/L) and the recovery was reported at higher levels (> 1200 mg/dL; 260.4 mmol/L)[18]. However, in the alcohol-dependent patients who develop a tolerance to alcohol as a result of the repeated exposure to ethanol, these effects may become reduced. This phenomenon seems to be related to the compensatory changes in excitatory *N*-methyl-*D*-aspartate and inhibitory gamma-amino-butyric acid (GABA)[19].

Acute alcohol intoxication can induce AH, usually in the subjects with chronic AUD and/or in the patients affected by alcoholic cirrhosis. Physical findings in the patients with AH include jaundice (the principal sign), hepatomegaly and spider angiomas. The symptoms may be non-specific which may involve fever, anorexia, weight loss, right upper quadrant pain, distension, or nausea and vomiting[20]. Alternatively, more severe symptoms can include encephalopathy and ascites.

PATHOGENESIS

The spectra of ALD are grouped into three histological stages: fatty liver, AH, and chronic hepatitis with fibrosis or cirrhosis. Fatty liver, the earliest response of the liver to alcohol abuse, is generally reversible with abstinence and is not believed to predispose to any chronic form of the liver disease if abstinence or moderation is maintained. AH develops in the patients with steatosis and is characterized by the presence of the inflammatory cells and hepatocellular injury with progressive fibrosis. In this case the reversibility is related to the degree of the liver injury. Finally, cirrhosis is irreversible and involves replacement of the normal hepatic parenchyma with extensive thick bands of fibrosis and regenerative nodules, which results in the clinical manifestations of portal hypertension and liver failure[21,22].

The toxic effect of alcohol on the liver is done by direct toxicity and an inflammatory cascade arising from portal venous translocation of Gram-negative bacteria due to increased small bowel permeability. The subsequent activation of Kupffer cell causes the release of reactive oxygen species and the production of various pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL) -7, IL-8, CXCL1, that lead to parenchymal neutrophil infiltration. Acetaldehyde, the alcohol metabolite, forms a variety of protein/DNA adducts that promote glutathione depletion, lipid peroxidation and mitochondrial damage[23].

DIAGNOSIS AND PROGNOSIS

AH generally occurs after decades of heavy AUD. Serum aminotransferase activities are typically five-to eight-fold elevated, the aspartate aminotransferase to alanine aminotransferase ratio is typically > 2, and serum bilirubin and alkaline phosphatise levels are generally elevated[3,18]. The differential diagnosis of suspected AH includes biliary obstruction, decompensated alcoholic cirrhosis, foamy fatty change, Zieve syndrome, drug-induced liver disease and acute viral hepatitis (*i.e.* hepatitis A or E). Serum bile acid concentrations are correlated with histology of AH in the patients with biopsy-proven disease. However, no consistent association between AH and cholestasis scores was observed[24].

The AH histopathological findings are characterised by the coexistence of macrovesicular steatosis, centrilobular ballooning of hepatocytes, infiltrate with polymorphonuclear leukocytes, Mallory bodies, megamitochondria and canalicular bile plugs[25]. The true reason of the incidence of AH is unclear. The published guidelines recommend histological confirmation of severe AH in the cases of diagnostic uncertainty[26]. Liver biopsy remains a useful tool in the diagnosis and

Table 1 Common scoring system used to predict prognosis in alcoholic hepatitis

Score name	Score formula				8- to 30-d mortality
Maddrey's discriminant function[31]	4.6 × [PT (s) - lab control PT (s)] + serum bilirubin (mg/dL)				Sensibility: 0.75 Specificity: 0.69
Model for end-stage liver disease[32]	3.78 × [Ln serum bilirubin (mg/dL)] + 11.2 × [Ln INR] + 9.57 × [Ln serum creatinine (mg/dL)] + 6.43				Sensibility: 0.69-0.75 Specificity: 0.68-0.75
Glasgow alcoholic hepatitis score[33]	Score given	1	2	3	Sensibility: 0.67 Specificity: 0.70
	Age	< 50	⩾ 50	-	
	WCC (10^9/L)	< 15	⩾ 15	-	
	Urea (mmol/L)	< 5	⩾ 5	-	
	PT ratio or INR	1.5	1.5-2.0	> 2.0	
	Bilirubin (μmol/L)	< 125	125-250	> 250	
ABIC score[34]	(age × 0.1) + [serum bilirubin (mg/dL) × 0.08] + [serum creatinine (mg/dL) × 0.3] + (INR × 0.8)				Sensibility: 0.92 Specificity: 0.32
Lille model score[35]	exp(-R)/[1 + exp(-R)][1]				Sensibility: 0.76 Specificity: 0.66

[1]*R* = 3.19-0.101 × (age in years) + 0.147 × (albumin day 0 in g/L) + 0.0165 × [bilirubin day 0 - bilirubin day 7 (mmol/L)] - 0.206 × (renal insufficiency) - 0.0065 × (bilirubin day 0 in mmol/L) - 0.0096 × (PT in seconds). PT: Prothrombin time; INR: International normalised ratio; WCC: White cell count.

management of severe AH, particularly when medical therapy is contemplated[27,28]. The prevalence of AH in the patients who undergo liver biopsy is of about 20% and it may be present in as many as 10%-35% of the hospitalized alcoholic patients[29,30]. Mild and moderate forms of AH frequently respond to alcoholic abstinence, whereas the prognosis of severe AH is poor; up to 40% die within 6 mo[31]. Especially in severe AH, even in the absence of cirrhosis, the portal system may come under the increased pressure because of liver scarring, resulting in portal hypertension and its complications.

The decision on how and when to treat the condition is pivotal and depends on the ability to establish the prognosis of the patients. Several scoring systems are available to assess the severity and prognosis of AH (Table 1). In particular, the modified Maddrey's discriminant function (MDF), the model for end-stage liver disease (MELD) score, the Glasgow alcoholic hepatitis score and the age-bilirubin-INR-creatinine (ABIC) score are utilized in the clinical practice[32-34].

The purpose of these scoring systems is to estimate the likelihood of short-term survival and to determine whether the patient should be treated with corticosteroids. The Lille score, instead, helps the physician to make the decision to stop corticosteroids after a week, or to continue for 28 d[35]. All scores use total bilirubin. The "weak point" of MDF is that requires the prothrombin time (PT) for the calculation. However, PT value can change between different laboratories[28,32]. This evidence has led to the development of new scoring systems. The MELD score, Glasgow, ABIC, and Lille score, all incorporating a measure of a kidney function, underscore the prognostic significance of an impaired kidney function in the patients with AH. In particular the MELD score includes the INR, which is standardized across laboratories, whereas the PT is not, and weighting of the INR and bilirubin level to reduce the influence of values at extremes[32].

MDF is the simplest and the most widely used score, validated by several groups as a reproducible criterion to identify the patients at a high risk of early mortality. Its score allows identification of those with non-life threatening AH (MDF < 32) who will recover with abstinence and who do not require specific treatment. Those with higher scores experience mortality of up to 50% in some studies and the recent clinical trials have addressed the management of the patients in this group. International guidelines report the use of MDF to estimate the likelihood of short-term survival as the primary endpoint. The MELD, the Glasgow, and the ABIC scores may be considered as alternative or additional tools to assess the disease severity.

PHARMACOTHERAPY

The optimal pharmacological treatment of severe AH is controversial and is one of the main challenges in the ALD. The development of the specific treatments has followed increasing understanding of the pathogenesis of this disease[36,37]. The key processes involve oxidative stress, inflammation and fibrosis. Secondary abnormalities include malnutrition and impaired hepatic regeneration. The specific treatment of the ALD is directed to acute injury in order to block the progression of the fibrosis. With a lifestyle modification, some studies support the treatment with glucocorticoids (GCs), pentoxifylline, anti-TNF-α, *S*-adenosylmethionine (SAMe) and antioxidants (Table 2).

Glucocorticoids

GCs are the first line treatment for severe AH. However, the efficacy of steroids has been debated for several decades and considered as the potential side effects that include anti-anabolism, muscular proteolysis, immunosuppression, increased susceptibility to the infections and increased risk of gastrointestinal bleeding. In addition, many patients with alcoholic diseases are predominantly obese, insulin resistant, or diabetic, and concomitant chronic hepatitis B or C is often present. In these settings, the clinical management with steroids are very

Table 2 Treatment considerations of severe alcoholic hepatitis

Treatment	Options	Comments
Corticosteroids	Prednisolone	If MDF ⩾ 32: 40 mg daily orally for 28 d followed by a 2/4-wk taper
Phosphodiesterase inhibitors	Pentoxyfilline	400 mg orally 3 times daily for 4 wk
Anti TNF-α	Infliximab	Infliximab 5 mg/kg *iv* at day 0 and prednisone 40 mg/d for 28 d (data not confirmed)
Nutrition	Eating, tube feeding	Diet rich in carbohydrate- and protein-derived calories; potassium replacement; vitamin supplementation
Antioxidant	Metadoxine	1500 mg/d orally for 3 mo
Antioxidant	*S*-adenosylmethionine	1200 mg/d orally in ambulatory patients
Alcohol abstinence	Rehab program	Reduce alcohol withdrawal symptoms, alcohol craving and intake, promote abstinence, evaluation for OLT program
	disulfiram, naltrexone, acamprosate, baclofen	

MDF: Maddrey's discriminant function; OLT: Orthotopic liver transplantation; TNF-α: Tumor necrosis factor-α.

difficult.

A meta-analysis at the beginning of the 90s, done by 11 randomized studies (10 of which were placebo controlled), suggested a beneficial role of GSs in the patients with severe AH with hepatic encephalopathy, but without active gastrointestinal bleeding by reducing short-term mortality[38]. A later analysis involving 12 controlled clinical trials, could not confirm these benefits, including the patients with encephalopathy[39]. In further support of this finding, the Cochrane review of 2008, including 15 randomized controlled trials with a total of 721 patients, concluded that GCs did not statistically reduce mortality compared with the placebo. A mortality benefit, however, was seen in a subgroup of the patients with MDF greater than 32 or with hepatic encephalopathy[40]. A successive meta-analysis was done using individual patient data from 5 randomised controlled trials. The patients were classified as complete responders (Lille score ⩽ 0.16), partial responders (Lille score between 0.16 and 0.56), and null responders (Lille score ⩾ 0.16). GCs improved 28-d survival in the patients' survival within the complete and partial responders, but not in the null responders[41].

Based on these data and on the clinical guidelines of the European Association for the Study of the Liver it is possible to make appropriate conclusions[42]. The GCs therapy of AH is limited by the concerns of heightened risks of sepsis and gastrointestinal hemorrhage. The patients with mild to moderate AH (MDF < 32), without hepatic encephalopathy and with the improvement in serum bilirubin or decline in the MDF score during the first week of hospitalization, should be monitored closely. Such patients will not likely require the benefit from the specific medical interventions and are expected to recover with nutritional support and abstinence from alcohol. The patients with severe disease (MDF ⩾ 32) with or without encephalopathy, who do not have contraindications to GCs, should be considered for a 4-wk treatment with prednisolone (40 mg/d), stopped or followed by a taper during 2-4 wk. Prednisolone is preferred to prednisone because the latter requires conversion to prednisolone in the liver, a process that may be impaired in AH. A new treatment is needed for the poor responders. Early liver transplantation may be considered after a careful selection process of these patients.

Pentoxifylline

Pentoxifylline is a phosphodiesterase inhibitor that blocks transcription of TNF-α to decrease serum levels of the gene product. It may be an acceptable therapeutic option in the patients with severe AH. When compared to the placebo, the patients with severe AH (MDF score ⩾ 32) treated with pentoxifylline presented a higher 6-mo survival. This was related to a marked decreased development of a hepatorenal syndrome[43]. Three randomized clinical trials compared pentoxifylline in combination with GCs and GCs monotherapy in severe AH[44-46]. However, these studies reported that the combination of GCs and pentoxifylline presented no additional survival advantage compared with GCs alone in a 6-mo survival. On the basis of these data, the guidelines by American Association for the Study of Liver Disease recommend pentoxifylline (400 mg orally 3 times daily for 4 wk) in the patients with severe AH (MDF score ⩾ 32), especially if there are contraindications to the GCs treatment[26,47]. The European Association for the Study of the Liver Guidelines recommend using pentoxifylline if sepsis precludes the use of GCs[42].

Anti TNF-α

TNF-α is a key cytokine that reproduces a number of features of alcoholic hepatitis. It is known to be increased in proportion to the severity of this disease and its low levels increase the liver regeneration[48]. The anti TNF-α therapies were considered as the most attractive strategies to treat severe AH. In a pilot study, 20 patients with biopsy-proved severe AH (MDF between 32 and 55) were randomized to either 5 mg/kg *iv* of infliximab at day zero plus 40 mg/d of prednisone or prednisone alone. In severe AH, infliximab was well tolerated and associated with a significant improvement of MDF score at day 28[49]. The effectiveness of anti-TNF-α was not confirmed in two randomized controlled trials testing multiple doses of infliximab (10 mg/kg in weeks 0, 2, 4, associated with prednisolone 40 mg/d for 28 d) or etanercept (25 mg *sc* 6 times over 3 wk), for association with a higher probability of severe infections and deaths[50,51]. In summary, the role of anti TNF-α agents

is limited in the confines of the approved randomized clinical trials.

Metadoxine

One specific drug that is useful in the treatment of severe AH is metadoxine (pyridoxol *L*-2-pyrrolidone-5-carboxylate). Pyrrolidone carboxylate is involved in the amino acid metabolism through the glutathione pathway[52]. It facilitates de novo ATP synthesis and prevents ATP decrease in the brain and liver of rats acutely intoxicated with ethanol. Pyridoxine increases the metabolic degradation rate of ethanol, thereby reducing the damage to the cell functions caused by acetaldehyde, the first metabolite in the ethanol elimination process. It can also prevent glutathione depletion, lipid peroxidation damage, collagen deposition and TNF-α secretions induced by alcohol and acetaldehyde in hepatocytes and hepatic stellate cells[53]. A double-blind controlled trial included 136 alcoholic patients diagnosed with fatty liver who were randomly assigned to metadoxine (1500 mg/d) or placebo for 3 mo. A significant improvement in the liver function tests was reported in both groups at the end of the study. However, the improvement was observed more rapidly in those randomized to metadoxine[54]. More recently our group, in a retrospective study of 94 alcohol dependent patients, who received metadoxine for alcohol intoxication with a dose ranged between 500-2000 mg/d and a period of 2-42 d, registered a significant improvement in the transaminase levels, accompanied by the decrease in drinks per week and craving level[53]. Further studies are needed for better understanding of the potential role of metadoxine to treat the ALD, and, in particular, the severe forms of AH, and to define the exact dosage.

S-adenosylmethionine and other antioxidant

SAMe is a principal methyl donor for methyltransferase reactions that regulates gene expression and facilitates the generation of the antioxidant glutathione from homocysteine. The protective effects on the liver in the course of alcoholic injury are also mediated by the maintenance of mitochondrial function and down-regulation of TNF-α. Several data established the association of an abnormal hepatic methionine metabolism with the development of the ALD[55]. SAMe was studied in the patients with liver cirrhosis. In a multicenter randomized, double-blind trial, 123 patients were treated with SAMe (1200 mg/d, orally) or placebo for 2 years. Mortality was not reduced overall, but after the exclusion of a small number of very advanced cases with Childs C cirrhosis, a significant reduction in mortality was found. This study has yet to be replicated, but SAMe is used sporadically on the basis of these encouraging results and its safe profile[56]. Randomized, blinded, placebo-controlled studies assessed the effectiveness of Milk Thistle in chronic ALD. The results of these trials might be conflicting and confounded because of heterogeneity of the degree of the disease severity and alcoholic intake or abstinence[57]. Pre-clinical studies showed that silymarin, the active complex of this plant, play a role to protect against the acute liver injury caused by ethanol administration[58]. Considering its safety profile, it could be developed as an effective therapeutic agent for acute AH by its anti-oxidative stress and anti-inflammatory features. For ambulatory patients, the antioxidant therapies may be considered in a motivated patient with a specific nutritional support.

OTHER TREATMENTS

Nutrition

Alcoholic patients present a profound catabolic state with malnutrition, secondary to anorexia and poor diet, which can promote bacterial infections[59]. In fact, large volumes of alcohol suppress the appetite. Many admit that drinking is the main source of their calories in the form of alcohol. However, nutritional support is recommended in the patients with AH[60]. It improves the liver function and the obtained results from histological analyses might increase the survival rates based on the results of short-term follow-up studies. Nutrition should be provided orally or *via* a nasojejunal tube if nausea, vomiting, or encephalopathy are present. The patients with AH also require multivitamin, folic acid and thiamine supplementations. The formula of the enteral diet was a low-fat diet in which medium-chain triglycerides and oleic acid were accounted for most of its lipid content and rich in carbohydrate and protein-derived calories[61]. It was also suggested that combined treatment with enteral nutrition and GCs could improve the outcome of the patients with severe AH[62].

The maintenance of *ev* fluids should be avoided. These patients are often profoundly potassium depleted due to the lack of an intake of potassium-containing foods and hyperaldosteronism due to their liver disease. The replacement of potassium may be required daily until the serum potassium level is normal without supplementation. If the patients with AH exhibit signs of fluid retention, but the blood urea nitrogen and creatinine are normal, spironolactone may be given, which increases urinary excretion of sodium, water and serum potassium[63]. Oral furosemide may, then, be added, once the serum potassium normalizes without further need for potassium supplementation. If azotemia occurs, diuretics should be discontinued and the patients should be evaluated for a hepatorenal syndrome. There may be a component of malabsorption of vitamin K due to jaundice in addition to poor synthesis of coagulation components by the diseased liver. Three daily doses of vitamin K (10 mg) intravenously or subcutaneously usually decrease the international normalized ratio (INR). Oral dosing of vitamin K is not effective because of the poor absorption in the setting of deep jaundice[37]. Finally, considering the potential risk of Wernicke's encephalopathy, the supplementation with B-complex vitamins is needed[64].

Baclofen

Total alcohol abstinence represents the cornerstone in the treatment strategy for the patients affected by severe AH. This point in the clinical practice is often problematic, especially when these patients present a psychiatric diagnosis of AUD. Medical recommendations and/or brief interventions may not be sufficient to achieve and maintain the abstinence when a diagnosis of dependence is present. Therefore, the need to add pharmacological approaches has been emphasized in the last decades. As a consequence, pharmacotherapy of AUD is undergoing a period of the scientific development. Several drugs that can reduce alcohol craving, and consequently, can increase abstinence and prevent alcohol relapse have been evaluated[65]. In particular, disulfiram, naltrexone, and acamprosate have been approved for AUD. However, these medications might worsen liver disease[66].

Baclofen is a $GABA_B$ receptor antagonist that represents a new alcohol pharmacotherapy. Several preclinical and clinical studies demonstrated that baclofen could represent an effective drug to treat the AUD patients[67,68]. In particular, this drug was shown to reduce alcohol withdrawal symptoms, as well as to reduce alcohol craving and intake and to promote alcohol abstinence[69]. Notably, baclofen showed a safe profile when administered to the alcoholics, including those with liver cirrhosis. In a randomized, double-blind, controlled study, we evaluated the efficacy of baclofen for the maintenance of alcohol abstinence in 148 alcohol-dependent patients with liver cirrhosis. The subjects were randomized to either oral baclofen (10 mg 3 times a day) or placebo for 12 wk. Of 42 patients treated with baclofen, 71% achieved and maintained abstinence compared with 29% of 42 patients assigned to the placebo group[70]. The appropriate dosing of baclofen is still being debated. The secondary analysis with baclofen in the patients without underlying liver disease, have shown a dose-effect relationship of the drug on the reduction of daily alcohol intake and on the number of drinks per drinking day[69]. In this regard, it should be taken into account that the safety of the drug in the alcoholic patients with alcoholic hepatitis has also been reported recently by Avanesyan[71].

Liver transplantation

Orthotopic liver transplantation (OLT) is a possible therapeutic option for severe AH in the non-responder patients. The OLT is the last treatment option for the patients with end-stage liver disease who have a greater than 10% risk of dying[42]. The patients with severe AH who do not respond to GCs or pentoxifylline have a mortality of 50% to 75% within 6 mo[72]. Several Centers have proposed that this is a rescue option for the patients with severe AH who do not respond to medical therapies. However, the risk of recidivism of AUD still represents the major ethical concern about the usefulness of the OLT in alcoholic patients. The outcomes and in particular the survival rate, are better than other causes of the end-stage liver disease, especially if recidivism does not occur[73]. Even when the recidivism is present, the risks of developing the ALD and graft loss are unpredictable, due to the modifications in the susceptibility to alcohol damage secondary to the OLT. A period of 6-mo in total alcohol abstinence before the OLT is proposed as a strategy to reduce the risk of recidivism. However, this strategy is not evidence based and it is not accepted worldwide[65]. Recently, a prospective multicenter study showed that the early OLT clearly improved the 6-mo survival in the patients with a first episode of severe AH not responding to medical treatment[74]. In our opinion, the 6-mo rule should not be considered as a predictor of a recidivism risk, but as a recovery period. In particular, with all its limitations, the 6-mo rule should be used to test the possible improvement of liver function, which could avoid the OLT. When liver function does not allow for a 6-mo waiting time, such as in the patients with severe AH or with the advanced ALD, the pre-OLT abstinence time should be shortened, at least in the patients strictly followed by an alcohol addiction unit (AAU)[74,75]. The management of the alcoholic patients with the end-stage ALD listed for the OLT by an AAU within a liver transplant Centre could represent a useful strategy to reduce the risk of alcohol recidivism both before and after the transplantation.

FUTURE PERSPECTIVES

ALD remains one of the major medical problems in the individuals with AUD. The therapy of ALD and, in particular, of severe AH is a problem in a clinical practice due to the complex of the pathogenetic mechanisms. However, several options are now available and the use of several system scores to define the severity of the disease can guide the physician to make a treatment strategy in the function of the short-term survival. Recently, several basic and pre-clinical studies have started to define the cellular mechanisms involved in the liver disease progression and injury severity in a better way, including the high rates of apoptosis, lipid peroxidation, generation of free radicals and depletion of antioxidant capacity of the liver[76,77]. However, the results in animal models do not reproduce all the pathological changes found in humans with severe forms of the disease. In addition, translational research using human samples have identified novel potential therapeutic targets, but the prevailing pathogenetic pathways involved in the ALD are not defined and the innovations in the treatment approach are far to coming.

To the contrary, the most important goal of the therapy and the prevention in the ALD is abstinence from alcohol. In this regard, several data confirm the role of baclofen to reduce alcohol craving, particularly in the patients with the severe ALD. This drug is very interesting because it has a low level metabolism by the liver and appears to have few side effects, and presents the ability to maintain significantly a higher number of the patients

in abstinence which is beneficial in the treatment of the liver disease progression and/or to consider for the admission in an OLT program. To date, baclofen represents the only anti-craving medication formally tested in a randomized clinical trial in the alcoholic patients affected by liver cirrhosis, although additional confirmatory studies are warranted.

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