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Management of Non Alcoholic Fatty Liver Diseases and their Complications

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Abstract: There is a rapid raise in the metabolic risk factors in the general population and non-alcoholic fatty liver disease has become the most common cause of liver disease worldwide. Early detection of hepatotoxicity is extremely important because continued ingestion of the drug is often associated with a poor prognosis. Insulin resistance play a central role in the pathogenesis of Non Alcoholic Fatty Liver Disease (NAFLD); thus obesity, diabetes and the metabolic syndrome are frequently associated with the disease. Consequently, as these metabolic conditions emerge as major health problems in Western society, it is now accepted that NAFLD is the most common chronic liver condition in the Western world. The pathogenesis of non-alcoholic fatty liver disease is not completely understood and even if insulin resistance is a chief pathogenetic key, many other factors are implicated in both liver fat accumulation and disease progression to non-alcoholic steatohepatitis. There is, as up till now no firm evidence-based treatment for NAFLD. Therapy is currently directed at treating components of the metabolic syndrome which may also be valuable for the liver. Management is further complex by the inability to predict which patients will develop liver-related morbidity and thus benefit from treatment. Data were located, selected and extracted from SCI database, Medline, Pubmed, Highwire and Google Scholar.

Key words: Biopsy of liver, insulin sensitizers, lipid-lowering drugs, antioxidants and ursodeoxycholic acid, liver transplantation

INTRODUCTION

Dosage-dependent hepatotoxicity or adverse reactions to drugs used in therapeutic dosage may be the main culprit in the etiology of liver diseases (Alisi *et al.*, 2009). Early detection of hepatotoxicity is extremely important because continued ingestion of the drug is often associated with a poor prognosis (Bedogni *et al.*, 2005). Non-Alcoholic Fatty Liver Disease (NAFLD) is most oftenly diagnosed liver disease in the world and the Western countries are considered to be commonly affected with it. NAFLD describes a syndrome of a broad spectrum of liver abnormalities, ranging from accumulation of fat (simple steatosis) to Non-Alcoholic Steatohepatitis (NASH), with varying degrees of inflammation and fibrosis, progressing to cryptogenic cirrhosis (George and Farrell, 2005).

Presently, NAFLD is regarded as the liver manifestation of the metabolic syndrome and is strongly associated with obesity, insulin resistance, hypertension and dyslipidaemia. Now there is rapid growth in clinical and basic studies in NAFLD due to increased spread of the obesity 'pandemic' in adults and children and it is also realised that the outcomes of obesity-related liver disease are not entirely benign (Targher *et al.*, 2006).

Depending on the underlying pathogenesis NAFLD may be categorized as primary or secondary (Table 1). Primary NAFLD occurs most commonly and is mainly associated with insulin-resistant states, such as diabetes and obesity. Presently, the term 'secondary' NAFLD is not used and the other preferred nomenclature includes the known causative factor and the resultant pathology, e.g., total parenteral nutrition-induced, drug-induced steatosis/steatohepatitis (Targher *et al.*, 2005). Data were located, selected and extracted from SCI database, Medline, Pubmed, Highwire and Google Scholar.

Table 1: Categories of nonalcoholic fatty liver disease

Category	Associations
Primary	Obesity, glucose intolerance, hypertension, hypertriglyceridemia, low HDL cholesterol
Secondary	Corticosteroids, tamoxifen, diltiazem, aspirin, HAART, Drugs valproate, amiodarone, methotrexate, total parental nutrition
Viruses conditions	Hepatitis C, human immunodeficiency virus Metabolic Hypobetalipoproteinemia, lipodystrophy, Nutritional hypopituitarism, hypothalamic obesity, Weber Christian syndrome, acute fatty liver of pregnancy, Reyes syndrome
Toxins	Organic solvents, mushroom toxins
Nutritional	Rapid weight loss, intestinal bypass surgery, starvation

DISEASE ASSOCIATIONS WITH NAFLD

Cardiovascular disease: Given the close association between NAFLD and classical cardiovascular risk factors, it may not be surprising that, when compared to controls, patients with NAFLD often associated with atherosclerosis, as shown by increased carotid wall intimal thickness, increased numbers of atherosclerotic plaques and increased plasma markers of endothelial dysfunction (Fracanzani *et al.*, 2008). This association also extends to children as the occurrence of coronary and aortic atheroma is higher in children with fatty liver compared to controls in an autopsy-based report (Sanyal *et al.*, 2006). Consistent with these observations two natural history studies have revealed that the increased age-related mortality observed in patients with NAFLD is attributable to cardiovascular as well as liver-related deaths (Targher *et al.*, 2007). As an indirect association between NAFLD and cardiovascular disease is expected, a growing body of evidence supports a direct role for NAFLD in the pathogenesis of atheromatous cardiovascular disease. A cohort study of patients with T2DM reported that the prevalence of cardiovascular, cerebrovascular and peripheral vascular disease was considerably greater in those with NAFLD than in those without independent of the individual components of the metabolic syndrome (Schwimmer *et al.*, 2005). Related findings have also been observed for microvascular diseases, nephropathy and retinopathy. The mechanism of any direct effect of NAFLD on cardiovascular risk is yet to be determined; possibilities include the release of atherogenic inflammatory cytokines and pro-coagulant factors from the steatotic liver (Cerdeira *et al.*, 2007).

Polycystic ovary syndrome (PCOS): As with the association between NAFLD and the metabolic syndrome, now the well-established association between NAFLD and PCOS expected to be indirect as a result of both conditions being characterised by insulin resistance. Up to 30% of females with PCOS have raised Alanine Transaminase (ALT) levels and a NAFLD prevalence of 42% has been reported in a series of PCOS patients with a mean age of 25 years (Setji *et al.*, 2006; Wolk and Somers, 2006). More advanced fibrotic liver disease has been reported in patients with PCOS, these emerging evidences suggest that women with this syndrome require careful hepatic evaluation (Tanne *et al.*, 2005).

Obstructive sleep apnoea (OSA): Chronic intermittent hypoxia, as observed in Obstructive Sleep Apnoea (OSA),

has been associated with cardiovascular disease, the metabolic syndrome and insulin resistance (Guerrero *et al.*, 2009). As might be expected, therefore, a proportion of patients with OSA have raised liver enzymes and histological features of NASH independent of body weight (Alisi *et al.*, 2009). The severity of histology and the associated insulin resistance both correlate with the severity of OSA, strongly implicating insulin resistance as the pathogenic mechanism relating OSA to NASH although not completely excluding a role for hypoxic liver injury. As with PCOS, this and other related reports propose that patients with OSA require hepatic evaluation and that the diagnosis of OSA should be considered in NAFLD patients reporting daytime somnolence, sleep disturbances or any other symptoms suggesting a diagnosis of OSA (Alisi *et al.*, 2009).

EPIDEMIOLOGY

The prevalence of NAFLD is 14-16% in Asians, 31-33% in African-Americans and Caucasians and 45% among Hispanics, differences partially explained by different visceral adiposity distribution (Mummadi *et al.*, 2008). Metabolic disorders raise the risk of NAFLD, occurring in 65-70% of obese and diabetic and in up to 96% of morbidly obese subjects (Kallwitz *et al.*, 2007). Beside overall risk of NAFLD, metabolic factors impact also the intensity of liver disease: NASH affects 3% of the general population, 20-30% of obese and diabetic and 35-40% of morbidly obese subjects (Targher *et al.*, 2005). The presence of OSAS, as well, raises the risk of NASH by fourfold in morbidly obese patients, independently of overweight whether chronic intermittent hypoxia promotes liver injury necessitates further prospective investigation (Petta *et al.*, 2009).

PATHOPHYSIOLOGY

Mechanisms underlying hepatic fat accumulation: In NAFLD patients liver fat derives from dietary Free Fatty Acids (FFA) and from two other phenomena-both mainly dependent on IR, namely liver FFA influx and liver de novo lipogenesis. The authors also highlighted a significant increase in de novo lipogenesis from 5% in healthy subjects to 26% in NAFLD and noted that about 15% of liver fat obtained from dietary FFA. Human studies have clearly confirmed a considerable increase in serum FFA in NAFLD patients compared to controls, specifically an increase of palmitate release from adipose tissue into plasma, an expression of lipolysis, associated with a

compensatory increase in VLDL-TG secretion, even if not sufficient to control intrahepatic fat content. Here it is important to note that FFA liver influx is strongly regulated by saturable plasmamembrane protein transporters such as caveolins, Fatty Acid Transport Proteins (FATPs), Fatty Acid Translocase (FAT/CD36) and Fatty Acid Binding Proteins (FABPs), all of which could be considered for future research (Wagenknecht *et al.*, 2009).

ROLE OF GENETICS IN NAFLD

Two cohort studies and one community-based study in different ethnicities evaluated the heritability of NAFLD to reach 35-40% of the total predisposition, even after adjusting for age, gender, race and BMI (Schwimmer *et al.*, 2009). Many important gene modulating steps of hepatic glucose and lipid metabolism, inflammation and fibrogenesis, that have been discussed in the pathogenesis section, have been candidate by small cohort studies and are reviewed elsewhere (Romeo *et al.*, 2008). Two independent genome-wide association population-based studies and three smaller group studies found the missense variant rs738409 (encoding I148M) in the Patatin-like Phospholipase 3 (PNPLA3) gene encoding adiponutrin is associated with hepatic steatosis across different ethnic groups and independently of obesity and diabetes status (Yuan *et al.*, 2008). Adiponutrin is a transmembrane protein with phospholipase, TG lipase and acylglycerol transacylase activity (transfers fatty acids to mono- and di-acylglycerol), expressed in liver and adipocytes, whose biological significance is not completely known which is induced during adipocyte differentiation and in response to fasting and peroxisome proliferator-activated receptor-g (PPAR-g) activation and is down-regulated by insulin and TNF- α (Trombini and Piperno, 2007).

DIAGNOSTIC ISSUES

If the individual is not affected with advanced disease, the routine liver blood tests are either normal or typically show mild elevations of transaminases, alkaline phosphatase and Gamma Glutamyl Transpeptidase (GGT) 1.5-3 x the upper limit of normal. The ALT/AST ratio is greater than 1 except there is advanced fibrotic NAFLD or the patient is a covert heavy drinker. Other blood tests are mainly used to detect associated conditions, such as dyslipidaemia and excluding alternative causes of abnormal liver blood tests. Regarding lipids, it is important to measure serum levels of apolipoprotein B (Apo-B) in patients either with no obvious risk factors for NAFLD

or with low levels of LDL and HDL cholesterol, looking for evidence of hypobetalipoproteinemia which is a rare and familial cause of NAFLD. Increased levels of Serum ferritin often found in NAFLD patients and have been associated with advanced fibrosis. HFE genotyping should be carried out when hyperferritemia is accompanied by increased transferrin saturation. Auto-antibodies linked with Autoimmune Hepatitis (AIH), including ANA and SMA, are frequently present at low titres in patients with NAFLD and have been associated with more advanced disease in some but not all, studies (Loria *et al.*, 2005). Around 1 in 10 of these patients has histological features of autoimmune hepatitis on biopsy and accomplishes diagnostic criteria for probable/definite AIH. Currently available imaging modalities including ultrasound, CT and routine MR imaging are all excellent at detecting steatosis (once more than around a third of the liver is affected) but no one can reliably identify NASH or fibrosis. Modern imaging techniques including proton magnetic resonance spectroscopy and transient elastography show promise but needs further study prior to routine use for disease staging (Cox *et al.*, 2006).

THE BIOPSY OF LIVER

Undoubtedly the most important and controversial issue to consider in the investigation of patients with suspected NAFLD is whether to perform a liver biopsy or not. For diagnosis, biopsy is not compulsory for a "typical" patient with abnormal liver blood tests, classical risk factors for NAFLD (obesity, T2DM, dyslipidemia) and an ultrasound showing steatosis, however, a high ferritin with HFE mutations, positive autoantibodies (ANA, SMA) or the use of medications associated with drug-induced liver injury all may justify a biopsy to avoid alternative/additional diagnoses. The main indication to perform a biopsy is, however, the accurate staging of the disease since (a) different stages have different prognoses so it require different management strategies and (b) presently available imaging techniques can't perform this role (Saadeh *et al.*, 2002).

NON-INVASIVE MARKERS FOR STAGING NAFLD

The current reliance on liver biopsy for disease staging has driven many studies aimed at defining clinical or laboratory-based variables capable of acting as surrogate markers of disease stage (Guha *et al.*, 2006). Various clinical and laboratory markers have been revealed to be associated with advanced fibrosis (bridging fibrosis or cirrhosis) in patients with NAFLD, particularly advanced age (>45 years), BMI > 30 kg m⁻²,

T2DM (or raised fasting blood glucose), the severity of OSA an AST:ALT ratio greater than 1, hyperferritinemia and positive autoantibodies. At present, it would therefore, seem reasonable to confine liver biopsy to patients with at least some, if not all, of these risk factors. Some of these markers (age, BMI, T2DM, AST/ALT ratio) have been combined together with platelet count and serum albumin concentration, into a NAFLD fibrosis “score” that precisely predicts the presence or absence of advanced fibrosis in the majority of patients with NAFLD (Angulo *et al.*, 2007). This score has been combined with the European Liver Fibrosis (ELF) panel of serum fibrosis markers and proved to have an accuracy of over 90% in differentiating different fibrosis stages in NAFLD (Guha *et al.*, 2008).

In case of non-invasive diagnosis of NASH rather than fibrosis stage, serum levels of a caspase cleavage product of the hepatocyte protein cytoke- ratin-18 (a putative marker of hepatocyte apoptosis) have been shown to accurately predict the presence of NASH in a small pilot study. Undoubtedly this and other tests and scoring systems require further validation before they can be used in routine clinical practice but they do appear, at last, to offer real potential to replace the necessity of liver biopsy in the majority of patients with NAFLD (Wieckowska *et al.*, 2006).

Treatment: Treatment algorithm, treatment options and pharmacological classification of drugs used for management of NAFLD are illustrated in Fig. 1-3.

WEIGHT REDUCTION

Diet and exercise: Many small, mostly uncontrolled, studies have shown an improvement in either ALT or steatosis following diet (with or without exercise)-induced weight loss. There is no but very little evidence that necroinflammation or fibrosis can be improved by weight loss only though a few small case series have shown some improvement in these parameters with severe weight loss (Harrison and Day, 2007). Till now, almost all studies of diet-induced weight loss have simply employed restriction on calorie intake, with very few attempting to manipulate particular dietary components. This area seems worthy of study, as intake of both saturated fat and fibre are known to influence insulin resistance and diets high in saturated fat, soft drinks and meat and low in omega 3-containing fish also known to be associated with both NAFLD and NASH. Dietary fat consumption can also be correlate with liver fat content and insulin resistance in short-term studies of obese, non-diabetic women-independently of changes in total-body, subcutaneous or abdominal fat. The importance of exercise in achieving and maintaining weight loss and improving insulin resistance is well recognized and so far the only controlled study of weight loss that has reported histological improvement (steatosis) combined calorie restriction with increased exercise (Westerbacka *et al.*, 2005).

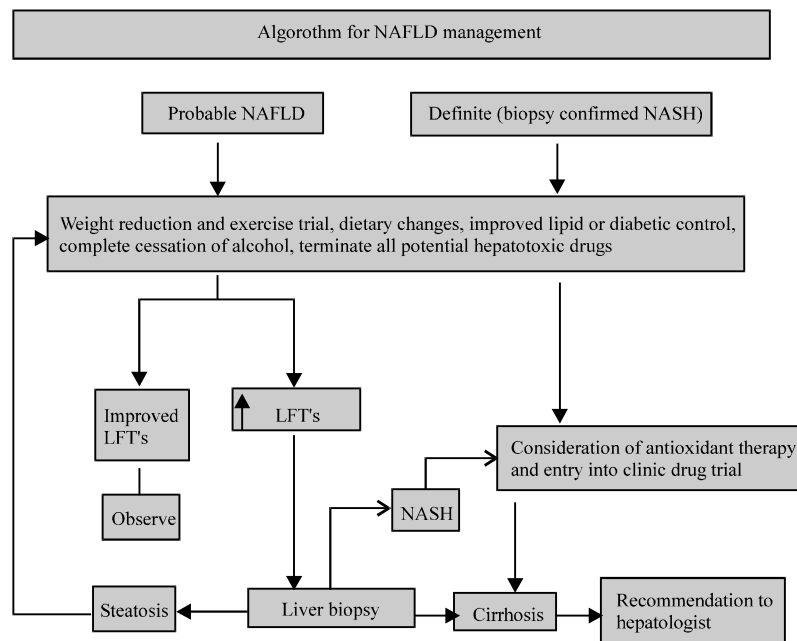


Fig. 1: Algorithm for NAFLD Management

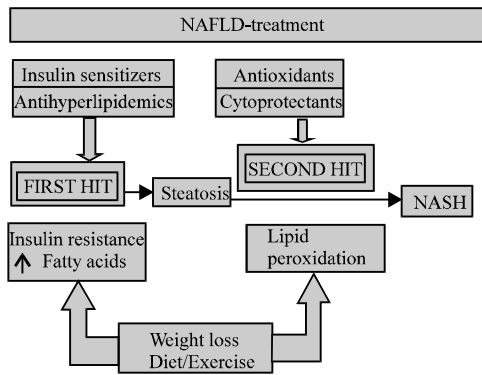


Fig. 2: NAFLD treatment

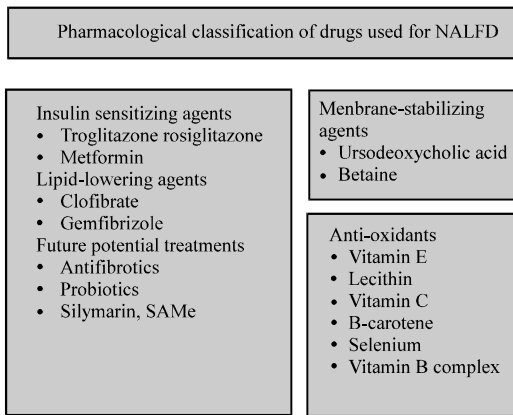


Fig. 3: Pharmacological classification of drugs used for NAFLD

Pharmacological anti-obesity agents: Promoting improvements in liver histology have been reported from pilot studies of the intestinal lipase inhibitor orlistat in patients with NASH, however, till now there is no proof that this improvement is superior to what would be expected from the resulting weight loss. However, data from presently ongoing large RCTs of orlistat are awaited with interest (Hussein *et al.*, 2007).

Bariatric surgery: Various measures including surgical procedures are currently in use for the treatment of obesity. Biliopancreatic diversion have a considerable risk of liver failure and worsening fibrosis and should therefore be avoided in patients with NAFLD, however, more hopeful results have been reported for gastric bypass and gastric banding surgery. Till now, all studies have shown improvements in metabolic parameters and steatosis with some but not all, reporting improvements in necroinflammation and fibrosis (Dixon *et al.*, 2004).

INSULIN SENSITIZERS

Metformin: Pilot studies of metformin in diabetic and non-diabetic patients with NAFLD have reported inconsistent effects on liver blood tests and steatosis (determined by MRI or MR proton spectroscopy). Though, the largest RCT to date, in non-diabetic NAFLD patients, has been more encouraging. In this 12 month, randomised open-label trial, metformin treatment (2 g day^{-1}) was associated with significantly higher rates of normalised aminotransferase levels and with considerable decreases in liver fat, necroinflammation and fibrosis, compared with either Vitamin E treatment or a weight-reducing diet treated patients. The low number of patients who convinced to a second biopsy does, however, limit the strength of the conclusions that can be drawn from this study (Bugianesi *et al.*, 2005).

Thiazolidinediones (TZDs): TZDs are well known as agonists for the Peroxisome Proliferator Activated Receptor c (PPARc). They improve insulin sensitivity, at least partially, via anti-steatotic effects in the liver and muscle which may in turn result from an increased secretion of the anti-inflammatory, antifibrotic adipokine, adiponectin by adipocytes. In addition, their potential as a therapy for NAFLD is further increased by indication from animal models that they may also exert direct anti-fibrotic effects in the liver. Pilot studies of the second-generation TZDs, pioglitazone and rosiglitazone, have constantly reported encouraging improvements in insulin sensitivity and presently liver blood tests, liver histology and several large RCTs are in progress. The first placebo-controlled RCT of pioglitazone in the treatment of patients with NASH has reported significant improvement in steatosis, inflammation and ballooning necrosis associated with a non-insignificant decrease in fibrosis. Now-a-days caution over the use of TZDs in the treatment of NASH has been increased as a result of several meta-analyses of trials of TZDs in T2DM patients that have consistently shown that rosiglitazone increases the risk of myocardial infarction and heart failure (Singh *et al.*, 2007). Moreover, the possibility of heart failure is also increased by pioglitazone but it is associated with a lower risk of myocardial infarction and stroke compared to placebo-treated patients (Lincoff *et al.*, 2007).

LIPID-LOWERING DRUGS

Atherogenic dyslipidemia is always associated with NAFLD as part of the metabolic syndrome. Hence, the

potential therapeutic role of lipid-lowering drugs in NAFLD has been explored. A controlled trial with the fibrate gemfibrozil 600 mg daily for 4 weeks showed some biochemical improvement in NAFLD, while clofibrate has not produced any biochemical or histological improvement. In a small RCT, Probucol, a lipid-lowering agent with strong antioxidant properties has improved liver enzymes in NASH. In uncontrolled trials it is found that HMG-CoA reductase inhibitors like pravastatin and atorvastatin are safe, improves serum aminotransferases in NAFLD and also showed beneficial effects on necroinflammation in two studies (Gomez-Dominguez *et al.*, 2006). A RCT randomized 186 hyperlipidemic NAFLD patients to atorvastatin, fenofibrate, or both (Athysos *et al.*, 2006). Each arm received lifestyle intervention. Following one year, weight loss in all arms averaged 11-13% but biochemical plus ultrasonographic regression of NAFLD was significantly elevated with atorvastatin alone or in combination, than with fenofibrate. In a small placebo-controlled RCT, it was found that administration of simvastatin for one year was safe but did not improve any histological feature in NASH. An important issue concerning the use of statins in-patients with NAFLD is their potential hepatotoxicity. After analysing existing data, a consensus panel concluded that patients with NAFLD are not at significantly increased risk of severe hepatic toxicity with standard doses of statins and these drugs can be safely used in-patients with NAFLD (Chalasani, 2005).

HYPERTENSION

No RCTs have particularly studied the effect of different anti-hypertensive agents on the liver in hypertensive patients with NAFLD. However, a growing body of evidence from animal models of hepatic fibrosis and NASH suggests that therapy focussed at the renin-angiotensin system and a-blockers may be encouraging for the liver. To date only one pilot study has examined the use of angiotensin II receptor blockade in patients with NASH and showed a reduction in serum markers of fibrosis. Novel angiotensin II receptor blockers with insulin sensitising effects appear worthy of study in NAFLD (Ichikawa, 2007).

ANTIOXIDANTS AND URSODEOXYCHOLIC ACID (UDCA)

As oxidative stress is thought to be the second hit leading to inflammation in NASH, antioxidant Vitamin E and C have been evaluated in animal and human models,

producing controversial results. An analysis on an intention-to-treat basis of six RCTs concluded that despite the significant improvements in liver enzymes and minor adverse events, radiological and histological data are too inadequate to support or repudiate the use of antioxidants in-patients with NAFLD. In a 24 month RCT, the administration of vitamin E and UDCA for 24 months significantly improved steatosis but not other histological features, compared with either agent alone, in NASH. The UDCA causes the reduction in portion of hydrophobic bile acids contributing to oxidative stress. A number of clinical trials, of which only one assessed histology and had a low-bias risk, have been conducted in NAFLD. No significant variations in the degree of steatosis, inflammation or fibrosis could be observed between the treated and placebo arms (Dufour *et al.*, 2006). Iribhogbe *et al.* (2011) showed that Vitamin A, C and E monotherapy is useful in management of NAFLD.

ENDOCANNABINOID RECEPTOR ANTAGONISTS

Rimonabant antagonizes cannabinoid type 1 (CB1) receptors in the central nervous system and the liver leading to reduction in food and caloric intake and inhibiting hepatic DNL and stellate cell activation. In a subgroup of abdominally obese dyslipidemic patients from the An International Study of Rimonabant in Dyslipidemia with AtheroGenic Risk in Abdominally Obese Patients (ADAGIO)-Lipids trial, rimonabant appreciably improved hepatic steatosis and all cardiometabolic risk factors compared with placebo. Adverse effects which lead to discontinuation of the drug involve gastrointestinal, depressive (2.0% vs. 1.3% of placebo) and anxiety disorders (2.2% vs. 1.0%). Due to the development of suicidal tendency associated with depressive and anxiety disorders, Food and Drug Administration (FDA) refused approval of rimonabant in the USA (Despres *et al.*, 2009).

ANGIOTENSIN II TYPE 1 RECEPTOR BLOCKERS

Preclinical studies showed a marked reduction in hepatic, insulin resistance, steatosis and fibrosis and stellate cell activation with angiotensin II type 1 receptor blockers (ARBs). Telmisartan and irbesartan also have PPAR-g agonism activity, thus improving insulin sensitivity experimentally (Hirose *et al.*, 2007). In humans, angiotensin II type 1 receptor polymorphisms have been associated with the existence and severity of NAFLD. These findings and the frequent coexistence of

hypertension with NAFLD encouraged evaluation of ARBs in NAFLD. Following the enthusiastic results of two uncontrolled trials with losartan, 54 hypertensive patients with NASH were randomized to telmisartan or valsartan. After 20 months it was found that both agents improved blood pressure and steatosis to a similar extent but telmisartan improved plasma lipids, insulin sensitivity, steatosis, necroinflammation and fibrosis more consistently than valsartan. Larger- and longer-duration RCTs will evaluate the efficacy of ARB with PPAR-g activity in the treatment of NASH (Georgescu *et al.*, 2009).

ANTI-CYTOKINE AGENTS

Beneficial effects of anti-TNF α in NASH therapy have been demonstrated in preclinical studies and two clinical studies in patients with NAFLD have reported improvements in aminotransferase levels and histology. As the importance of pro-inflammatory cytokines in both liver pathology and insulin resistance in obesity has been established, it seems likely that cytokines and their regulatory molecules will become major therapeutic targets in both NAFLD and T2DM in the near future (Satapathy *et al.*, 2007).

OTHER AGENTS

Efforts to develop pharmacologic means for hepatic protection from damage during regeneration have identified a few molecular targets. It has newly been shown that pentoxifylline (Trental, Hoechst-Roussel), an inhibitor of TNF- α synthesis in Kupffer cells that has other properties such as vasodilatation and induction of the interleukin-6 pathway, reduces the likelihood of inadequate liver function in the liver remnant in a murine model of partial liver transplantation (Ansari and Jamil, 2011).

LIVER TRANSPLANTATION

No specific antidote is available for the majority of hepatotoxic agents. Emergency liver transplantation has increasing usefulness in the setting of drug-induced fulminant hepatotoxicity. Bearing in mind early liver transplantation is important. The model for End-Stage Liver Disease score can be employed to evaluate short-term survival in an adult with end-stage liver disease. This can help stratify candidates for liver transplantation. The parameters employed are serum creatinine, total bilirubin, international normalized ratio and the cause of the cirrhosis (Ansari, 2010).

Indications for liver transplantation in NASH-related cirrhosis are similar as other aetiologies. Compared with the latter, patients with NASH showed a tendency for high 1-year mortality, particularly if having age 60 years, obesity, diabetes or hypertension (Malik *et al.*, 2009). NASH recurs in 50% of patients within 4 years, depending on higher insulin resistance or steroid use, post-transplantation weight gain, diabetes, highlighting the significance of controlling metabolic risk factors to reduce disease relapse (Burke and Lucey, 2004).

HERBAL THERAPY OF NAFLD

According to the World Health Organization (WHO), about three-quarters of the world population depends upon herbal remedies for the health care of its people. The usage of plants, plant extracts or plant-derived pure chemicals for disease management, become a therapeutic modality which has stood the test of time (Ansari and Inamdar, 2010).

It has been reported that about 170 phytoconstituents isolated from 110 plants belonging to 55 families were stated to possess liver protective activity about 600 commercial herbal formulations with claimed hepatic protective activity are being marketed worldwide. Several hundred plants have been examined for use in a wide variety of liver disorders. Just a handful has been fairly well researched. The latter category of plants include: *Silybum marianum* (milk thistle), *Picrorhiza kurroa* (kutkin), *Curcuma longa* (turmeric), *Camellia sinensis* (green tea), *Chelidonium majus* (greater celandine), *Glycyrrhiza glabra* (licorice) and *Allium sativa* (garlic). Some complex Chinese herbal formulae, such as Pro-liver Pill (Yanggan Wan), Liver Care (Himalaya Drug Co, Bangalore, India), Liv-52, Jianpi Wenshen Pill (Jianpi Wenshen Wan), Binggan capsules (Binggan Jiaonang), Binggan Tang, Yizhu decoction (Yizhu Koufuye), Yiergan Tang and Xiaochaihu Tang (Sho-saiko-to or SST), have been reported to have significant therapeutic effects on liver protection or treatment of liver diseases (Ansari *et al.*, 2011).

CONCLUSION

At present, a diagnosis of NAFLD should prompt a thorough metabolic and cardiovascular risk evaluation to correct associated cardiometabolic risk factors but there is no indication that improving NAFLD would benefit cardiometabolic and liver-related morbidity and mortality in the long term. There is also urgent need for effective and accessible non-invasive methods to evaluate the

severity of liver disease in NAFLD. Future sufficiently powered RCTs with histological end points, of suitable duration will clarify long-term safety and efficacy of projected treatments.

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