Which Treatment for Nonalcoholic Fatty Liver Disease?

S. Moscatiello, R. Marzocchi, N. Villanova, E. Bugianesi and G. Marchesini*

Unit of Clinical Dietetics, "Alma Mater Studiorum" University, Bologna, and Department of Gastroenterology, University, Turin, Italy

Abstract: Subjects with nonalcoholic fatty liver disease are at risk of progressive liver failure. Lifestyle changes including weight-loss strategies and increased physical activity remain the first-line approach, but a few pharmacological treatments have also been successfully tested. Several drugs improve biochemistry, only a few improve histology; in all cases, the results were not sustained after treatment stop. Pharmacological treatment is not so far indicated outside controlled clinical trials with histological outcomes.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is now recognized as the most common cause of liver dysfunction in Western countries [1]. Hepatic fat accumulation is considered the hepatic manifestation of the metabolic syndrome [2,3] and it is closely associated with all its features, including insulin resistance, central adiposity, impaired glucose tolerance, hypertension and dyslipidemia [4,5]. The spectrum of NAFLD ranges from simple steatosis (fatty liver), considered a benign condition, to non-alcoholic steatohepatitis (NASH), potentially progressing to advanced fibrosis, cirrhosis and eventually hepatocellular carcinoma [6]. Accordingly, there is large interest in identifying treatments that may prevent or halt disease progression.

Intervention strategies have mainly focused on the modification of risk factors which are the basis of the metabolic syndrome. Lifestyle change (weight loss and/or exercise) is the mainstay in non-pharmacological intervention, and it should also represents the standard care in pharmacological trials. Any hypothesis on the pathogenesis of NAFLD is largely speculative, but the metabolic abnormalities associated with insulin resistance play a pivotal role both for the accumulation of fatty acids in the liver cells [7,8], as well as for progressive hepatocellular injury *via* the generation of oxidative stress and necroinflammation [9], apoptosis and fibrogenesis [10]. Mitochondrial dysfunction, iron overload and increased activity of cytochrome P450 2E1 promoting oxidative stress, as well as hormonal and cytokine imbalance, have been proposed in different models. It is also possible that hepatic fat accumulation *per se* may trigger disease progression, via a different lipid composition [11]. All these mechanisms forms the rationale for the various therapeutic approaches summarized in Table **1**.

TREATMENT OF THE METABOLIC SYNDROME

Weight Loss and Physical Activity

Given the association between obesity and insulin resistance, all NAFLD patients with overweight or obesity should undergo a weight management program. The American Gastroenterological Association recommends a target weight loss of 10% baseline weight as initial goal in all subjects whose BMI exceeds 25 kg/m^2. Weight reduction should be achieved by caloric restriction from dieting and increased physical activity, with a caloric deficit of 500 kcal/die, and should proceed at a rate of 0.5 kg/wk. More rapid weight loss (>1.6 kg/wk) due to a very low energy diet has been associated with exacerbation of NASH in obese patients [12], due to massive mobilization of fatty acids from visceral stores and their paradoxical hepatic accumulation.

In the short term, food intake and exercise may be easily modified, but the long-term adherence to prescriptive changes is difficult to achieve. A nutritional program based on cognitive-behavioral therapy leads to more sustained long-term lifestyle modifications than a prescriptive diet or a pharmacological approach to weight loss [13]. Similar programs have been successfully tested in NAFLD patients [14], and there is evidence that they may also be effective at population level [15]. Even if weight loss has a rational physiologic basis, the widely-held belief that weight reduction is an effective therapy for non-alcoholic fatty liver challenged [16], because of difficulties in implementing large, properly controlled trials carried out according to the principles of behavior therapy. Weight loss remains the first line-treatment, but effective weight loss programs cannot be carried out in the majority of Liver Units because of time and space constraints [17].

Also the composition of the diet might have a role in the pathogenesis and/or treatment. Patients with NAFLD seem more likely to have a diet high in refined sugars [18] or high in saturated fats and cholesterol and low in fibers and antioxidants [19]. Dietary counseling should include a reduction of dietary carbohydrates, and a preference towards monounsaturated fatty acids [20].

Weight loss improves both liver enzymes and histology [21], but physical activity *per se* has an addictive effect [22], enhancing muscle insulin sensitivity and is pivotal in most successful long-term weight loss program [23]. Gradual weight reduction and increased physical activity in overweight patients with liver disease not only improve liver enzymes [24], but also reduce serum insulin levels, and qual-

*Address correspondence to this author at the Unit of Clinical Dietetics, "Alma Mater Studiorum" University of Bologna, Policlinico S. Orsola, Via Massarenti, 9, I-40138 Bologna, Italy; E-mail: giulio.marchesini@unibo.it

1389-5575/08 $55.00+.00

Table 1. Pathophysiology-Based Treatment of NAFLD

Mechanism	Target	Treatment
Metabolic Syndrome	*Visceral obesity*	Diet & Exercise, Orlistat, Sibutramine, Rimonabant, Bariatric surgery
	Insulin resistance Diabetes	Metformin, Glitazones, Exercise, Nateglinide
	Hypertriglyceridaemia Low HDL-cholesterol	Clofibrate, Probucol, Statins, Gemfibrozil, ω-3 Fatty Acids
	Hypertension	Losartan
Lipid peroxidation	*Oxidative stress*	Vitamin E, Betaine, S-Adenosyl-L-methionine
	Cytoprotection	Ursodeoxycholic acid
	Iron overload	Phlebotomy
	Bacterial overgrowth	Probiotics/prebiotics
Cytokine imbalance	*High levels of proinflammatory cytokines*	Pentoxifylline
Hepatocyte death	*Increased apoptosis*	Caspase inhibitors

ity of life [25]. The optimal amount of exercise necessary to sustain long-term weight loss has yet to be determined [26].

In patients with BMI >35 kg/m^2 and obesity-associated comorbidities, bariatric surgery may also be considered for more aggressive weight management. Early reports showed that malabsorptive bariatric procedures, often associated with a dramatic weight loss, had deleterious effects on liver disease [27]. However, recent studies using different techniques (restrictive interventions) to promote a slower and less extensive weight loss (laparoscopic adjustable gastric banding, gastric by pass) showed that the biochemical and histological abnormalities associated with NASH are reversed by surgery, decreasing the hepatic expression of factors involved in the progression of NAFLD [28, 29]. In experienced hands, also the bilio-intestinal bypass procedure is effective and not accompanied by deleterious effects, improving liver injury even in subjects with advanced NAFLD stages [30].

Drug-Induced Weight Loss

There are theoretical reasons to postulate that medications favoring weight loss might also be effective at improving NAFLD, and a few studies are available (Table **2**) [31-34]. Currently, only two drugs are approved by the Food and Drug Administration for long-term use in weight loss programs, orlistat and sibutramine, and another is pending (rimonabant).

Orlistat, a lipase inhibitor, reduces dietary fat absorption by approximately 30%. A small pilot study showed an improvement in aminotransferases with a mean 10 kg weight

Table 2. Clinical Studies with Anti-Obesity Drugs in Subjects with Nonalcoholic Fatty Liver Disease

Authors [Ref.]	Study Type	Intervention (Daily Dose)	Control Arm (Daily Dose)	Number of Cases	Time of Study	Clinical and Biochemical Data*	Histological Improvement*
Harrison [31]	Case series	Orlistat (120 mg tid)	---	10	6 mo	Reduced BMI and ALT/AST	Steatosis in 6 cases, fibrosis in 3
Sabuncu [32]	Parallel case series	Orlistat (120 mg tid)	Sibutramine (20 mg)	13 + 13	6 mo	Similar ALT improvements in the two arms	N/A
Hatzitolios [33]	Case series	Orlistat (120mg tid) in obese	---	21	24 wks	Normal ALT in 100%	N/A
Zelber-Sagi [34]	Blind RCT	Orlistat (120 mg tid) + behavior	Placebo + behavior	44 (40 biopsies)	6 mo	Identical weight loss; ALT improvement	Steatosis (22 second biopsies)

* In randomized, controlled trials (RCT), the changes in clinical and biochemical data and histological improvements were considered by comparison between groups. N/A = Not assessed.

loss after six months of orlistat [35], with positive effects on liver histology too. In obese NAFLD patients with dyslipidemia, orlistat normalized aminotransferase levels and fatty liver was no longer present at ultrasounds in 86% of patients [33]. In a randomized, double-blind, placebo-controlled 6-month study on NAFLD patients confirmed by liver biopsy, orlistat, associated with a behavioral program, almost doubled the improvement in aminotransferase levels (48% vs 26%), and a statistically significant reversal of fatty liver was only observed in the orlistat arm. The beneficial effects of orlistat on serum biochemistry and steatosis were independent of weight reduction [34]. The mechanism of orlistat is mediated by malabsorption, carrying out a potential risk of fat-soluble vitamin deficiency, which might require adequate supplementation to avoid oxidative stress.

Sibutramine, a serotonin and norepinephrine reuptake inhibitor, enhances satiety. Its use was associated with weight loss and improvement in aminotransferases in NAFLD [32], and the amount of weight loss was similar to that observed on orlistat. In nearly all cases, steatosis was reduced at ultrasounds, but histology was not checked by repeated biopsies.

Rimonabant, an antagonist of the cannabinoid receptor subtype 1 (CB1), has potent anti-obesity effects and improves several features of obesity-associated diseases. It reduces food intake, body weight, fat mass, and hyperinsulinemia and ameliorates insulin sensitivity and plasma lipid levels in man [36,37], also reducing pro-inflammatory cytokines and increasing adiponectin. Very recently, rimonabant was shown to improve aminotransferases, dyslipidemia, hepatomegaly, TNF-α and adiponectin in obese *fa/fa* rats, suggesting that the drug might be potentially useful also in patients with steatosis.

In summary, there are very few data supporting an uncontrolled use of weight loss drugs in NAFLD patients. Randomized, controlled long-term studies are needed to assess the benefits of their long-term use on liver histology and disease progression.

Insulin-Sensitizing Drugs

Given the clear-cut relationship between fatty liver disease and the hyperinsulinemia/insulin resistance syndrome, any attempt to improve insulin sensitivity is expected to improve NAFLD, and insulin sensitizers have been extensively investigated (Table **3**) [38-48] (Fig. **1**).

Metformin improves insulin resistance and hyperinsulinemia by decreasing hepatic glucose production and by

Table 3. Clinical Studies with Insulin Sensitizers in Subjects with Nonalcoholic Fatty Liver Disease

Authors [Ref.]	Study Type	Intervention (Daily Dose)	Control Arm (Daily Dose)	Number of Cases	Time of Study	Clinical and Biochemical Data*	Histological Improvement*
Marchesini [38]	Pilot	Metformin (500mg tid)	---	14	4 mo	Normal ALT in 50%; reduced liver volume	N/A
Nair [39]	Pilot	Metformin (20mg/kg)	---	15	1 yr	No change	No change
Uygun [40]	Open label, randomized	Metformin (850mg bid)	Diet	17+17	6 mo	Normal ALT in 59% vs. 37%	No significant changes
Duseja [41]	Case series	Metformin	---	7	6 mo	Normal ALT in 58%	N/A
Bugianesi [42]	Open label, randomized	Metformin (850mg bid)	Vit. E (400 IU bid) or prescriptive diet	55+28+27	1 yr	Improved ALT	Steatosis, inflammation and fibrosis in 12 second biopsies in metformin
Schwimmer [43]	Pilot in children	Metformin (500 mg bid)	---	10	24 wks	Normal ALT in 40%	(Steatosis by MRI spectroscopy)
Caldwell [44]	Pilot	Troglitazone (400mg)	---	10	6 mo	Normal ALT in 70%	Necroinflammation in 6 cases
Neuschwander-Tetri [45]	Pilot	Rosiglitazone (4mg bid)	---	25	11 mo	Improved ALT	Steatosis and inflammation, not fibrosis
Promrat [46]	Pilot	Pioglitazone (30mg)	---	18	11 mo	Improved ALT (normal in 72%)	Steatosis, inflammation and fibrosis
Sanyal [47]	Open label, randomized	Pioglitazone (30mg) + Vit. E (400 IU)	Vit. E (400 IU)	8+10	6 mo	No change	Steatosis, inflammation and fibrosis
Belfort [48]	Blind RCT	Pioglitazone (45mg) + diet	Placebo + diet	55	6 mo	Improved ALT	Steatosis, inflammation and fibrosis

* In randomized, controlled trials (RCT), the changes in clinical and biochemical data and histological improvements were considered by comparison between groups. N/A = Not assessed.

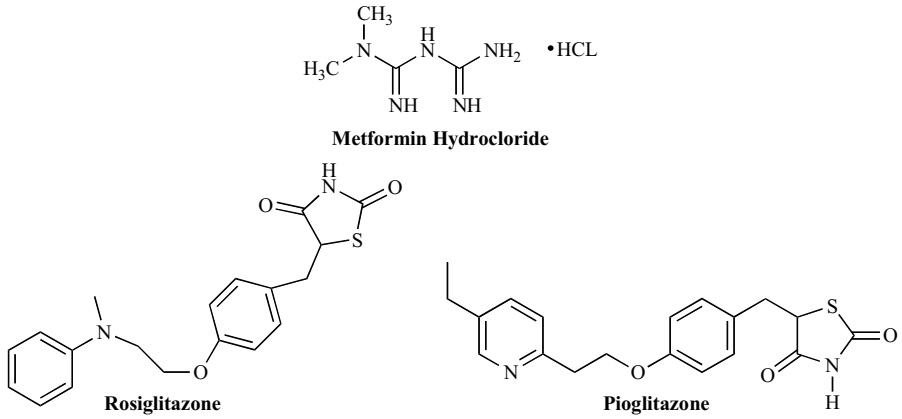

Fig. (1). Structures of insulin-sensitizing drugs.

increasing muscle glucose uptake. In animal models of fatty liver, metformin improved hepatic steatosis [49], and this was the basis for a series of controlled studies in humans. Metformin (500 mg tid for 4 months) moderately improved insulin sensitivity, normalized aminotransferase levels in 50% of cases and significantly reduced liver volume, but treatment withdrawal was accompanied by a return of aminotransferase to pre-treatment values [38]. These beneficial effects were confirmed, with a remarkable exception [39], in the following studies [40-42]. Changes in aminotransferase levels and insulin sensitivity achieved by metformin were greater than those obtained by dietary advice alone and were associated with improved necroinflammation at histology, and no return of aminotransferase levels to pre treatment values in a post-treatment follow-up of 6-12 months [40]. In non-diabetic NAFLD, metformin was more effective than alternative treatments (vitamin E or prescriptive diet) on aminotransferase levels, also improving the grading and staging of histological lesions in a few patients who had a post-treatment biopsy assessment [42]. Finally, metformin favored aminotransferase normalization in obese adults with NAFLD [41], as well as in NAFLD obese children [43], where it reduced liver fat, measured by magnetic resonance spectroscopy, insulin resistance and improved quality of life.

Glitazones improve insulin sensitivity predominantly in adipose tissue by activating the nuclear transcription factor, peroxisome proliferator-activated receptor-γ (PPAR-γ) [50]. Two glitazones are now under scrutiny in NAFLD patients, rosiglitazone and pioglitazone, after the first generation glitazone (troglitazone) was withdrawn from the market because of a severe idiopathic hepatitis. Curiously, while on the market, also troglitazone was effective on aminotransferase levels [44].

Rosiglitazone and pioglitazone have been evaluated in two pilot trials [45, 46]. Both drugs improve aminotransferases, insulin sensitivity, hepatic steatosis and the histological features of hepatic inflammation, compared with baseline. Pioglitazone, but not rosiglitazone was associated with improvement in the overall fibrosis stage. When added to vitamin E, pioglitazone improved steatosis, cytologic ballooning, Mallory hyaline and pericellular fibrosis [47], whereas vitamin E had no effects. Finally, a very recent placebo-controlled study in NASH confirmed that pioglitazone produces a remarkable improvement in metabolic profile and histology [48], but also the effects of glitazones on hepatic biochemistry seems to depend on continuous treatment [45, 51]. At histology, pioglitazone discontinuation was accompanied by worsening of steatosis and necroinflammation, without significant changes in fibrosis in a 48-week follow-up [51].

Lipid Lowering Drugs

Approximately 80% of NAFLD patients have elevated cholesterol and triglyceride levels; accordingly, several investigators have tested the effects of lipid-lowering drugs to reduce lipid levels and their potential burden to the liver (Table **4**) [33, 52-56]. Among the fibrate class, clofibrate was ineffective [52], whereas gemfibrozil was significantly more effective than placebo on aminotransferase levels, irrespective of baseline triglyceride levels [53].

More recently, statins, namely atorvastatin or pravastatin, were studied in limited pilot studies. A significant improvement in cholesterol and liver enzymes was reported with atorvastatin [54, 56], associated with changes at ultrasonography, but changes in fibrosis and necroinflammation were no better than those observed with UDCA. Atorvastatin was also more effective than ω-3 fatty acids, but less than orlistat, in improving hepatic enzymes levels and US echo-pattern [33]. Pravastatin normalized liver enzymes and improved hepatic inflammation in five NASH patients [55].

The lack of adequate randomized trial data and histological follow-up for these drugs make their role uncertain in the treatment of NAFLD. However, they remain a drug of choice in NAFLD with pronounced hyperlipidemia and are mandatory in subjects with high cardiovascular risk [57].

PREVENTION AND TREATMENT OF LIPID PEROXIDATION

Antioxidants and Cytoprotective Agents

Lipid peroxidation and secondary cellular injury are the putative mechanisms leading to progression from fatty liver to NASH. Uncontrolled lipid peroxidation generates free radicals producing mitochondrial abnormalities [58], hepato-

Table 4. Clinical Studies with Lipid-Lowering Agents in Nonalcoholic Fatty Liver Disease

Authors [Ref.]	Study Type	Intervention (Daily Dose)	Control Arm (Daily Dose)	Number of Cases	Time of Study	Clinics and Biochemistry*	Histological Improvement*
Laurin [52]	Pilot	Clofibrate (2g)	---	16	1yr	No change	No change
Basaranoglu [53]	Blind RCT	Gemfibrozil (600mg)	Placebo	23+23	4 wks	Improved ALT	N/A
Kiyici [54]	Open label	Atorvastatin (10mg) in hyper-lipidemics	UDCA (13-15mg) in normo-lipidemics	27	6 mo	Improved ALT	Steatosis at US
Hatzitolios [33]	Case series	Atorvastatin (20mg) in hyper- cholesterolemics	---	28	24 wks	Improved ALT	N/A
Rallidis [55]	Pilot	Pravastatin (20mg)	---	5	6 mo	Improved ALT	Steatosis and inflammation (4 second biopsies)
Gomez-Dominguez [56]	Pilot	Atorvastatin in hyper-lipidemics		22	1 yr	Normal ALT in 36%. Improved cholesterol	N/A
Hatzitolios [33]	Case series	ω-3 fatty acids (1200mg tid)	---	23	24 wks	Improved ALT	N/A

* In randomized, controlled trials (RCT), the changes in clinical and biochemical data and histological improvements were considered by comparison between groups. N/A = Not assessed.

cyte injury and cellular apoptosis [59]. Antioxidant agents, by breaking the chain of events which generate lipid peroxidation, and cytoprotective agents, by stabilizing cellular phospholipid membranes, might be effective in the treatment of NAFLD/NASH (Table **5**) [52, 60-72].

Vitamin E is a cheap and well-tolerated, potent antioxidant, and it is particularly attractive for NAFLD treatment in children. However, conflicting results have so far been reported in pilot [60] and controlled studies [61]. In adults, vitamin E is not better than placebo in three studies [42, 47, 62], whereas a 1-year vitamin E supplementation superimposed to nutritional counseling improved steatosis, inflammation and fibrosis [63]. Interestingly, whereas subjects with pure fatty liver obtained beneficial effects by diet-induced weight loss, patients with NASH improved liver enzymes only when vitamin E was added to behavioral changes. Finally, combination treatment with vitamin E and C was as effective as ursodeoxycholic acid (UDCA) – a drug of largely unproven efficacy (see below) – in a randomized, controlled study [65], and improved fibrosis, not necroinflammation in another [64]. High-dose (>400 IU/die), long-term vitamin E therapy has been recently associated with an increase in all-cause of mortality, thus challenging the notion of a harmless treatment [73].

Betaine, a natural component of the metabolic cycle of methionine, was previously shown to decrease hepatic steatosis in alcoholic hepatitis [74] possibly via increased S-adenosylmethionine levels and phosphatidylcholine production. In an open label trial, betaine improved or normalized aminotransferase and produced histological improvement in NAFLD [66], and in a larger study betaine glucuronate combined with other anti-oxidants was better than placebo both on liver enzymes and ultrasonography-assessed hepatic steatosis [67].

Probucol, a lipid-lowering drug with potent antioxidant properties, has been tested in a single NAFLD trial with positive results on enzyme levels [68], but the drug has been withdrawn from the market in Australia and USA because of its pro-arrythmic potential.

Ursodeoxycholic acid (UDCA) is by far the drug with cytoprotective, immunomodulatory and antiapoptotic properties most largely tested in NAFLD. Following a few positive reports [52, 75, 76], a case series in pediatric patients did not confirm the efficacy of UDCA [71] and a large placebo-controlled, randomized trial found no additional effect over placebo on liver biochemistry and histology after 2 years of treatment [69]. More recently, a combined treatment with UDCA+vitamin E proved to be superior to control arms (UDCA+placebo and placebo+placebo), suggesting that this issue is not settled [72].

FUTURE TREATMENTS

Other drugs have been tested because of their potential effects on intra-hepatic lipids, via different mechanisms (Table **6**) [77-82].

Circulating levels of tumor necrosis factor-α (TNF-α) are elevated in NASH patients [83], and an over-expression of TNF-α mRNA, both in the liver and in the adipose tissue, has been documented in severely obese patients with NASH [84]. Aminotransferases improved in a pilot trial of pentoxifylline, a TNF-α inhibitor [77], and the biochemical changes were mirrored by the histological resolution of steatosis, and improved inflammation and fibrosis stage during long-term pentoxifylline treatment [79].

Table 5. Clinical Studies with Anti-Oxidants and Cytoprotective Agents in Nonalcoholic Fatty Liver Disease

Authors [Ref.]	Study Type	Intervention (Daily Dose)	Control Arm (Daily Dose)	Number of Cases	Time of Study	Clinics and Biochemical Data*	Histological Improvement*
Lavine [60]	Pilot (in children)	Vit. E (400-1200mg)	---	11	5 mo	Improved ALT	N/A
Vajro [61]	Blind RCT (in children)	Vit. E (100-400 IU) + diet	Placebo + diet	14+14	5 mo	No change	N/A
Kugelmas [62]	Open label, randomized	Vit. E (800 IU) + diet & exercise	Diet & exercise	9+7	3 mo	No change	N/A
Hasegawa [63]	Pilot	Vit. E (300mg)	---	22	1 yr	Improved ALT in Fatty liver, not in NASH	No change
Harrison [64]	Blind RCT	Vit. E + Vit. C (1000mg +1000mg)	Placebo	23+22	6 mo	No change	Fibrosis
Ersoz [65]	RCT	Vit. E (600 IU) + Vit. C (500mg)	UDCA (10mg/kg)	28+29	6 mo	Normal ALT in 63% vs. 55%	N/A
Abdelmalek [66]	Pilot	Betaine (10g bid)	---	7	1 yr	Improved	Marginal (6 second biopsies)
Miglio [67]	Open label, randomized	Betaine, Diethanolamine, Nicotinamide (150mg + 30mg + 20mg) bid	Diet	191	1 yr	Improved	Steatosis
Merat [68]	Blind RCT	Probucol (500mg)	Placebo	18+9	6 mo	Normal ALT, 56% vs. 0%	N/A
Laurin [52]	Pilot	UDCA (15mg/kg)	---	19	1 yr	Improved	Steatosis
Lindor [69]	Blind RCT	UDCA (13-15mg/kg)	Placebo	56+65	2 yrs	No difference in ALT change	No difference
Mendez-Sanchez [70]	Blind RCT	UDCA (1200 mg)	Placebo	14+13	6 wks	Similar changes in ALT and BMI	N/A
Vajro [71]	Case series (in children)	UDCA (10mg/kg)	---	14	---	Improvement related to weight loss	N/A
Dufour [72]	Blind RCT	UDCA (12-15mg/kg) + Vit. E 400IU bid)	UDCA (12-15mg/kg/)+ Plac or Plac+Plac	15+18+15	2 yrs	Normal ALT, 53% vs. 28% vs. 20%	Steatosis

* In randomized, controlled trials (RCT), the changes in clinical and biochemical data and histological improvements were considered by comparison between groups. N/A = Not assessed.

Given that apoptosis is the mechanism of cell death in NAFLD [59], inhibitors of caspases, the proteases that initiate apoptosis, are of potential interest. Very recently, an anti-apoptotic caspase inhibitor was reported to produce ALT improvement in a short, double-blind, placebo-controlled, dose-ranging study including NASH patients [85], but many more studies are needed to verity the effectiveness and safety of this type of treatment.

In an animal model, intestinal-derived bacterial endotoxins sensitize fatty liver to the effect of TNF-α with subsequent liver damage [86]. The manipulation of the intestinal flora induces a significant beneficial effect in patients with various types and degree of chronic liver disease [87]. Administration of a probiotic to NAFLD patients over three months improved ALT as well as markers of lipid peroxidation [81].

Finally, there is a proven association between NAFLD and hyperferritinemia, iron overload and insulin resistance [88,89]. Insulin stimulates ferritin synthesis and facilitates iron uptake, leading to iron overload in both hepatocytes and sinusoidal cells [90]. Conversely, iron influences insulin signaling [91], reduces the hepatic extraction and the metabolism of insulin leading to peripheral hyperinsulinemia, and may increase the cellular oxidative stress, by inhibiting the internalization and action of insulin [92]. Increased hepatic iron and excessive fat accumulation may interact to generate the oxidative stress responsible for liver injury.

Phlebotomy is a well-tolerated treatment that was reported to improve insulin resistance in a small number of NAFLD patients without iron overload and either impaired [93] or normal [94] glucose tolerance. Treatment to near-iron

Table 6. Other Drugs Used in the Treatment of Nonalcoholic Fatty Liver Disease

Authors [Ref.]	Study Type	Intervention (Daily Dose)	Control Arm (Daily Dose)	Number of Cases	Time of Study	Clinics and Biochemistry*	Histological Improvement*
Satapathy [77]	Pilot	Pentoxifylline (400 mg tid)	---	18	6 mo	Improved ALT (normal in 60%) and fatigue	N/A
Adams [78]	Pilot	Pentoxifylline (1600 mg)	---	11 (9/20 withdrew)	1 yr	Improved ALT	N/A
Satapahy [79]	Pilot	Pentoxifylline (400 mg tid)	---	9	1 yr	Improved ALT and AST	Steatosis and lobular inflammation. Fibrosis in 4/6 with baseline fibrosis
Yokohama [80]	Pilot	Losartan (50mg)	---	7	48 wks	Improved ALT	Inflammation in 5, fibrosis in 4
Loguercio [81]	Case series	Probiotics	---	22	4 mo	Improved ALT	N/A
Morita [82]	Controlled study	Nateglinide (270 mg) in diabetics	Controls	5+5	20 wks	Improved ALT	Steatosis

In randomized, controlled trials (RCT), the changes in clinical and biochemical data and histological improvements were considered by comparison between groups. N/A = Not assessed.

deficiency improved aminotransferase, insulin and glucose levels, despite normal body iron stores at the beginning of the study, compared with nutritional counseling alone, independent of change in BMI, baseline insulin resistance, and the presence of the metabolic syndrome [95]. Long-term and biopsy-controlled studies are needed to prove the effectiveness and safety of phlebotomy in NAFLD patients.

CONCLUSIONS

Several questions arise when featuring an optimal pharmacologic and non-pharmacologic treatment of NAFLD, but most of these questions have no answer yet.

Firstly, disease progression is generally slow, only secondary to primary biliary cirrhosis in a report [96]. Any treatment should be tailored on patients' age and the presence of comorbidities, considering the relatively benign form of most cases.

Secondly, the disease is strictly associated with the metabolic syndrome and its underlying pathogenic mechanism(s): in order to cure the disease it would be pivotal to go the heart of the matter, and we know we are pretty far away from this goal. Any specific treatment of liver dysfunction is expected to lose its effects on discontinuation if the underlying mechanism is not resolved.

Thirdly, associated comorbidities (primarily, hypertension, diabetes and cardiovascular risk) should always be considered and generally they are priorities. This means that an integrated or, better, a team approach is the best answer to the complexity of disease, and it would be necessary for hepatologists to create links with other physicians who are responsible for care in these patients [17].

Finally, treatment should be cost/effective, and we have no long-term data on this issue. The cost of experimental treatment with new drugs in young, asymptomatic patients should always be weighed against the expected benefits at much older age. Very few controlled studies are so far available on histologic outcomes, and also in these cases treatment duration is too short to forecast long-term effects. This is the reason why we need carefully conducted long-term studies [97], and precise epidemiological follow-up of patients who had a histologic assessment.

A crucial issue remains obesity, whose treatment is far from optimal [98], and should be accompanied by strategies at population level; only through the synergy of individuals and a global societal response, the maximum benefit for NAFLD patients will be achieved.

In the absence of well-defined treatments, a rationale approach should start with a weight-loss behavioural program, including nutritional counselling and increased physical activity, associated with obesity drugs or even bariatric surgery when indications are fulfilled [99]. The control of associated comorbidities is also mandatory, primarily treatment of insulin resistance in prediabetes and overt diabetes, since obesity and diabetes remain the most significant risk factors for liver disease progression [100]. Any additional treatment should only be reserved to subjects entering randomized controlled trial.

REFERENCES

[1] Browning, J.D.; Szczepaniak, L.S.; Dobbins, R.; Nuremberg, P.; Horton, J.D.; Cohen, J.C.; Grundy, S.M.; Hobbs, H.H. *Hepatology*, **2004**, *40*, 1387.
[2] Marchesini, G.; Bugianesi, E.; Forlani, G.; Cerrelli, F.; Lenzi, M.; Manini, R.; Natale, S.; Vanni, E.; Villanova, N.; Melchionda, N.; Rizzetto, M. *Hepatology*, **2003**, *37*, 917.
[3] Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z. *Lancet*, **2005**, *365*, 1415.
[4] Angulo, P. *N. Engl. J. Med.*, **2002**, *346*, 1221.
[5] Clark, J.M.; Diehl, A.M. *Gastroenterology*, **2003**, *124*, 248.
[6] Falck-Ytter, Y.; Younossi, Z.M.; Marchesini, G.; McCullough, A.J. *Semin. Liver. Dis.*, **2001**, *21*, 17.

[7] Bray, G.A. *J Clin Endocrinol. Metab.*, **2004**, *89*, 2583.
[8] Donnelly, K.L.; Smith, C.I.; Schwarzenberg, S.J.; Jessurun, J.; Boldt, M.D.; Parks, E.J. *J. Clin. Invest.*, **2005**, *115*, 1343.
[9] Browning, J.D.; Horton, J.D. *J. Clin. Invest.*, **2004**, *114*, 147.
[10] Feldstein, A.E.; Gores, G.J. *Front. Biosci.*, **2005**, *10*, 3093.
[11] Puri, P.; Baillie, R.A.; Wiest, M.M.; Mirshahi, F.; Choudhury, J.; Cheung, O.; Sargeant, C.; Contos, M.J.; Sanyal, A.J. *Hepatology*, **2007**, *46*, 1081.
[12] Andersen, T.; Gluud, C.; Franzmann, M.B.; Christoffersen, P. *J. Hepatol.*, **1991**, *12*, 224.
[13] Clark, J.M. *J. Clin. Gastroenterol.*, **2006**, *40*, S39.
[14] Huang, M.A.; Greenson, J.K.; Chao, C.; Anderson, L.; Peterman, D.; Jacobson, J.; Emick, D.; Lok, A.S.; Conjeevaram, H.S. *Am. J. Gastroenterol.*, **2005**, *100*, 1072.
[15] Suzuki, A.; Lindor, K.; St Sauver, J.; Lymp, J.; Mendes, F.; Muto, A.; Okada, T.; Angulo, P. *J. Hepatol.*, **2005**, *43*, 1060.
[16] Wang, R.T.; Koretz, R.L.; Yee, H.F., Jr. *Am. J. Med.*, **2003**, *115*, 554.
[17] Bellentani, S.; Dalle Grave, R.; Suppini, A.; Marchesini, G. *Hepatology*, **2008**, *47*(2), 746.
[18] Solga, S.; Alkhuraishe, A.R.; Clark, J.M.; Torbenson, M.; Greenwald, A.; Diehl, A.M.; Magnuson, T. *Dig. Dis. Sci.*, **2004**, *49*, 1578.
[19] Musso, G.; Gambino, R.; De Michieli, F.; Cassader, M.; Rizzetto, M.; Durazzo, M.; Faga, E.; Silli, B.; Pagano, G. *Hepatology*, **2003**, *37*, 909.
[20] Archer, W.R.; Lamarche, B.; Deriaz, O.; Landry, N.; Corneau, L.; Despres, J.P.; Bergeron, J.; Couture, P.; Bergeron, N. *Obes. Res.*, **2003**, *11*, 978.
[21] Tilg, H.; Kaser, A. *Nat. Clin. Pract. Gastroenterol. Hepatol*., **2005**, *2,* 148.
[22] Cox, K.L.; Burke, V.; Morton, A.R.; Beilin, L.J.; Puddey, I.B. *Am. J. Clin. Nutr.*, **2004**, *80*, 308.
[23] Saris, W.H.; Blair, S.N.; van Baak, M.A.; Eaton, S.B.; Davies, P.S.; Di Pietro, L.; Fogelholm, M.; Rissanen, A.; Schoeller, D.; Swinburn, B.; Tremblay, A.; Westerterp, K.R.; Wyatt, H. *Obes. Rev.*, **2003**, *4*, 101.
[24] Ueno, T.; Sugawara, H.; Sujaku, K.; Hashimoto, O.; Tsuji, R.; Tamaki, S.; Torimura, T.; Inuzuka, S.; Sata, M.; Tanikawa, K. *J. Hepatol.*, **1997**, *27*, 103.
[25] Hickman, I.E.; Jonsson, J.R.; Prins, J.B.; Ash, S.; Purdie, D.M.; Clouston, A.D.; Powell, E.E. *Gut*, **2004**, *53*, 413.
[26] Jakicic, J.M.; Marcus, B.H.; Gallagher, K.I.; Napolitano, M.; Lang, W. *JAMA*, **2003**, *290,* 1323.
[27] Luyckx, F.H.; Desaive, C.; Thiry, A.; Dewe, W.; Scheen, A.J.; Gielen, J.E.; Lefebvre, P.J. *Int. J. Obes. Relat. Metab. Disord.*, **1998**, *22*, 222.
[28] Dixon, J.B.; Bhathal, P.S.; Hughes, N.R.; O'Brien, P.E. *Hepatology*, **2004**, *39*, 1647.
[29] Klein, S.; Mittendorfer, B.; Eagon, J.C.; Patterson, B.; Grant, L.; Feirt, N.; Seki, E.; Brenner, D.; Korenblat, K.; McCrea, J. *Gastroenterology*, **2006**, *130*, 1564.
[30] Mathurin, P.; Gonzalez, F.; Kerdraon, O.; Leteurtre, E.; Arnalsteen, L.; Hollebecque, A.; Louvet, A.; Dharancy, S.; Cocq, P.; Jany, T.; Boitard, J.; Deltenre, P.; Romon, M.; Pattou, F. *Gastroenterology*, **2006**, *130*, 1617.
[31] Harrison, S.A.; Ramrakhiani, S.; Brunt, E.M.; Anbari, M.A.; Cortese, C.; Bacon, B.R. *Am. J. Gastroenterol.*, **2003**, *98*, 926.
[32] Sabuncu, T.; Nazligul, Y.; Karaoglanoglu, M.; Ucar, E.; Kilic, F.B. *Rom. J. Gastroenterol.*, **2003**, *12*, 189.
[33] Hatzitolios, A.; Savopoulos, C.; Lazaraki, G.; Sidiropoulos, I.; Haritanti, P.; Lefkopoulos, A.; Karagiannopoulou, G.; Tzioufa, V.; Dimitrios, K. *Indian J. Gastroenterol.*, **2004**, *23*, 131.
[34] Zelber-Sagi, S.; Kessler, A.; Brazowsky, E.; Webb, M.; Lurie, Y.; Santo, M.; Leshno, M.; Blendis, L.; Halpern, Z.; Oren, R. *Clin. Gastroenterol. Hepatol.*, **2006**, *4*, 639.
[35] Harrison, S.A.; Fincke, C.; Helinski, D.; Torgerson, S.; Hayashi, P. *Aliment. Pharmacol. Ther.*, **2004**, *20*, 623.
[36] Despres, J.P.; Golay, A.; Sjostrom, L. *N. Engl. J. Med.*, **2005**, *353*, 2121.
[37] Pi-Sunyer, F.X.; Aronne, L.J.; Heshmati, H.M.; Devin, J.; Rosenstock, J. *JAMA*, **2006**, *295*, 761.
[38] Marchesini, G.; Brizi, M.; Bianchi, G.; Tomassetti, S.; Zoli, M.; Melchionda, N. *Lancet*, **2001**, *358*, 893.
[39] Nair, S.; Diehl, A.M.; Wiseman, M.; Farr, G.H., Jr.; Perrillo, R.P. *Aliment. Pharmacol. Ther.*, **2004**, *20*, 23.
[40] Uygun, A.; Kadayifci, A.; Isik, A.T.; Ozgurtas, T.; Deveci, S.; Tuzun, A.; Yesilova, Z.; Gulsen, M.; Dagalp, K. *Aliment. Pharmacol. Ther.*, **2004**, *19*, 537.
[41] Duseja, A.; Murlidharan, R.; Bhansali, A.; Sharma, S.; Das, A.; Das, R.; Chawla, Y. *Indian J. Gastroenterol.*, **2004**, *23*, 12.
[42] Bugianesi, E.; Gentilcore, E.; Manini, R.; Natale, S.; Vanni, E.; Villanova, N.; David, E.; Rizzetto, M.; Marchesini, G. *Am. J. Gastroenterol.*, **2005**, *100*, 1082.
[43] Schwimmer, J.B.; Middleton, M.S.; Deutsch, R.; Lavine, J.E. *Aliment. Pharmacol. Ther.*, **2005**, *21*, 871.
[44] Caldwell, S.H.; Hespenheide, E.E.; Redick, J.A.; Iezzoni, J.C.; Battle, E.H.; Sheppard, B.L. *Am. J. Gastroenterol.*, **2001**, *96*, 519.
[45] Neuschwander-Tetri, B.A.; Brunt, E.M.; Wehmeier, K.R.; Oliver, D.; Bacon, B.R. *Hepatology*, **2003**, *38*, 1008.
[46] Promrat, K.; Lutchman, G.; Uwaifo, G.I.; Freedman, R.J.; Soza, A.; Heller, T.; Doo, E.; Ghany, M.; Premkumar, A.; Park, Y.; Liang, T.J.; Yanovski, J.A.; Kleiner, D.E.; Hoofnagle, J.H. *Hepatology*, **2004**, *39*, 188.
[47] Sanyal, A.J.; Mofrad, P.S.; Contos, M.J.; Sargeant, C.; Luketic, V.A.; Sterling, R.K.; Stravitz, R.T.; Shiffman, M.L.; Clore, J.; Mills, A.S. *Clin. Gastroenterol. Hepatol.*, **2004**, *2*, 1107.
[48] Belfort, R.; Harrison, S.A.; Brown, K.; Darland, C.; Finch, J.; Hardies, J.; Balas, B.; Gastaldelli, A.; Tio, F.; Pulcini, J.; Berria, R.; Ma, J.Z.; Dwivedi, S.; Havranek, R.; Fincke, C.; DeFronzo, R.; Bannayan, G.A.; Schenker, S.; Cusi, K. *N. Engl. J. Med.*, **2006**, *355*, 2297.
[49] Lin, H.Z.; Yang, S.Q.; Chuckaree, C.; Kuhajda, F.; Ronnet, G.; Diehl, A.M. *Nat. Med.*, **2000**, *6*, 998.
[50] Yki-Jarvinen, H. *N. Engl. J. Med.*, **2004**, *351*, 1106.
[51] Lutchman, G.; Modi, A.; Kleiner, D.E.; Promrat, K.; Heller, T.; Ghany, M.; Borg, B.; Loomba, R.; Liang, T.J.; Premkumar, A.; Hoofnagle, J.H. *Hepatology*, **2007**, *46*, 424.
[52] Laurin, J.; Lindor, K.D.; Crippin, J.S.; Gossard, A.; Gores, G.J.; Ludwig, J.; Rakela, J.; McGill, D.B. *Hepatology*, **1996**, *23*, 1464.
[53] Basaranoglu, M.; Acbay, O.; Sonsuz, A. *J. Hepatol.*, **1999**, *31*, 384.
[54] Kiyici, M.; Gulten, M.; Gurel, S.; Nak, S.G.; Dolar, E.; Savci, G.; Adim, S.B.; Yerci, O.; Memik, F. *Can. J. Gastroenterol.*, **2003**, *17*, 713.
[55] Rallidis, L.S.; Drakoulis, C.K.; Parasi, A.S. *Atherosclerosis*, **2004**, *174*, 193.
[56] Gomez-Dominguez, E.; Gisbert, J.P.; Moreno-Monteagudo, J.A.; Garcia-Buey, L.; Moreno-Otero, R. *Aliment. Pharmacol. Ther.*, **2006**, *23*, 1643.
[57] Chalasani, N. *Hepatology*, **2005**, *41*, 690.
[58] Caldwell, S.H.; Chang, C.Y.; Nakamoto, R.K.; Krugner-Higby, L. *Clin. Liver. Dis.*, **2004**, *8*, 595.
[59] Feldstein, A.E.; Canbay, A.; Angulo, P.; Taniai, M.; Burgart, L.J.; Lindor, K.D.; Gores, G.J. *Gastroenterology*, **2003**, *125*, 437.
[60] Lavine, J.E. *J. Pediatr.*, **2000**, *136*, 734.
[61] Vajro, P.; Mandato, C.; Franzese, A.; Ciccimarra, E.; Lucariello, S.; Savoia, M.; Capuano, G.; Migliaro, F. *J. Pediatr. Gastroenterol. Nutr.*, **2004**, *38*, 48.
[62] Kugelmas, M.; Hill, D.B.; Vivian, B.; Marsano, L.; McClain, C.J. *Hepatology*, **2003**, *38*, 413.
[63] Hasegawa, T.; Yoneda, M.; Nakamura, K.; Makino, I.; Terano, A. *Aliment. Pharmacol. Ther.*, **2001**, *15*, 1667.
[64] Harrison, S.A.; Torgerson, S.; Hayashi, P.; Ward, J.; Schenker, S. *Am. J. Gastroenterol.*, **2003**, *98*, 2485.
[65] Ersoz, G.; Gunsar, F.; Karasu, Z.; Akay, S.; Batur, Y.; Akarca, U.S. *Turk. J. Gastroenterol.*, **2005**, *16*, 124.
[66] Abdelmalek, M.F.; Angulo, P.; Jorgensen, R.A.; Sylvestre, P.B.; Lindor, K.D. *Am. J.Gastroenterol.*, **2001**, *96*, 2711.
[67] Miglio, F.; Rovati, L.C.; Santoro, A.; Setnikar, I. *Arzneimittelforschung*, **2000**, *50*, 722.
[68] Merat, S.; Malekzadeh, R.; Sohrabi, M.R.; Sotoudeh, M.; Rakhshani, N.; Sohrabpour, A.A.; Naserimoghadam, S. *J. Hepatol.*, **2003**, *38*, 414.
[69] Lindor, K.D.; Kowdley, K.V.; Heathcote, E.J.; Harrison, M.E.; Jorgensen, R.; Angulo, P.; Lymp, J.F.; Burgart, L.; Colin, P. *Hepatology*, **2004**, *39*, 770.
[70] Mendez-Sanchez, N.; Gonzalez, V.; Chavez-Tapia, N.; Ramos, M.H.; Uribe, M. *Ann. Hepatol.*, **2004**, *3*, 108.

[71] Vajro, P.; Franzese, A.; Valerio, G.; Iannucci, M.P.; Aragione, N. *J. Pediatr.*, **2000**, *136*, 739.
[72] Dufour, J.F.; Oneta, C.M.; Gonvers, J.J.; Bihl, F.; Cerny, A.; Cereda, J.M.; Zala, J.F.; Helbling, B.; Steuerwald, M.; Zimmermann, A. *Clin. Gastroenterol. Hepatol.*, **2006**, *4*, 1537.
[73] Miller, E.R., 3rd; Pastor-Barriuso, R.; Dalal, D.; Riemersma, R.A.; Appel, L.J.; Guallar, E. *Ann. Intern. Med.*, **2005**, *142*, 37.
[74] Mato, J.M.; Camara, J.; Fernandez de Paz, J.; Caballeria, L.; Coll, S.; Caballero, A.; Garcia-Buey, L.; Beltran, J.; Benita, V.; Caballeria, J.; Sola, R.; Moreno-Otero, R.; Barrao, F.; Martin-Duce, A.; Correa, J.A.; Pares, A.; Barrao, E.; Garcia-Magaz, I.; Puerta, J.L.; Moreno, J.; Boissard, G.; Ortiz, P.; Rodes, J. *J. Hepatol.*, **1999**, *30*, 1081.
[75] Ceriani, R.; Bunati, S.; Morini, L.; Sacchi, E.; Colombo, G. *Hepatology*, **1998**, *28*, A386.
[76] Guma, G.; Viola, L.; Thome, M.; Galdame, O.; Alvarez, E. *Hepatology*, **1997**, *26*, A387.
[77] Satapathy, S.K.; Garg, S.; Chauhan, R.; Sakhuja, P.; Malhotra, V.; Sharma, B.C.; Sarin, S.K. *Am. J. Gastroenterol.*, **2004**, *99*, 1946.
[78] Adams, L.A.; Zein, C.O.; Angulo, P.; Lindor, K.D. *Am. J. Gastroenterol.*, **2004**, *99*, 2365.
[79] Satapathy, S.K.; Sakhuja, P.; Malhotra, V.; Sharma, B.C.; Sarin, S.K. *J. Gastroenterol. Hepatol.*, **2007**, *22*, 634.
[80] Yokohama, S.; Yoneda, M.; Haneda, M.; Okamoto, S.; Okada, M.; Aso, K.; Hasegawa, T.; Tokusashi, Y.; Miyokawa, N.; Nakamura, K. *Hepatology*, **2004**, *40*, 1222.
[81] Loguercio, C.; Federico, A.; Tuccillo, C.; Terracciano, F.; D'Auria, M.V.; De Simone, C.; Del Vecchio Blanco, C. *J. Clin. Gastroenterol.*, **2005**, *39*, 540.
[82] Morita, Y.; Ueno, T.; Sasaki, N.; Tateishi, Y.; Nagata, E.; Kage, M.; Sata, M. *Hepatogastroenterology*, **2005**, *52*, 1338.
[83] Wigg, A.J.; Roberts-Thomson, I.C.; Dymock, R.B.; McCarthy, P.J.; Grose, R.H.; Cummins, A.G. *Gut*, **2001**, *48*, 206.
[84] Crespo, J.; Cayon, A.; Fernandez-Gil, P.; Hernandez-Guerra, M.; Mayorga, M.; Dominguez-Diez, A.; Fernandez-Escalante, J.C.; Pons-Romero, F. *Hepatology*, **2001**, *34*, 1158.
[85] Pockros, P.J.; Schiff, E.R.; Shiffman, M.L.; McHutchison, J.G.; Gish, R.G.; Afdhal, N.H.; Makhviladze, M.; Huyghe, M.; Hecht, D.; Oltersdorf, T.; Shapiro, D.A. *Hepatology*, **2007**, *46*, 324.
[86] Yang, S.Q.; Lin, H.Z.; Lane, M.D.; Clemens, M.; Diehl, A.M. *Proc. Natl. Acad. Sci. USA*, **1997**, *94*, 2557.
[87] Loguercio, C.; De Simone, T.; Federico, A.; Terracciano, F.; Tuccillo, C.; Di Chicco, M.; Carteni, M. *Am. J. Gastroenterol.*, **2002**, *97*, 2144.
[88] Bugianesi, E.; Manzini, P.; D'Antico, S.; Vanni, E.; Longo, F.; Leone, N.; Massarenti, P.; Piga, A.; Marchesini, G.; Rizzetto, M. *Hepatology*, **2004**, *39*, 179.
[89] Mendler, M.H.; Turlin, B.; Moirand, R.; Jouanolle, A.M.; Sapey, T.; Guyader, D.; Le Gall, J.Y.; Brissot, P.; David, V.; Deugnier, Y. *Gastroenterology*, **1999**, *117*, 1155.
[90] Turlin, B.; Mendler, M.H.; Moirand, R.; Guyader, D.; Guillygomarc'h, A.; Deugnier, Y. *Am. J. Clin. Pathol.*, **2001**, *116*, 263.
[91] Fargion, S.; Dongiovanni, P.; Guzzo, A.; Colombo, S.; Valenti, L.; Fracanzani, A.L. *Aliment. Pharmacol. Ther.*, **2005**, *22 (Suppl 2)*, 61.
[92] Houstis, N.; Rosen, E.D.; Lander, E.S. *Nature*, **2006**, *440*, 944.
[93] Facchini, F.S.; Hua, N.W.; Stoohs, R.A. *Gastroenterology*, **2002**, *122*, 931.
[94] Valenti, L.; Fracanzani, A.L.; Fargion, S. *Gastroenterology*, **2003**, *124*, 866; author reply 866.
[95] Valenti, L.; Fracanzani, A.L.; Dongiovanni, P.; Bugianesi, E.; Marchesini, G.; Manzini, P.; Vanni, E.; Fargion, S. *Am. J. Gastroenterol.*, **2007**, *102*, 1251.
[96] Poynard, T.; Mathurin, P.; Lai, C.L.; Guyader, D.; Poupon, R.; Tainturier, M.H.; Myers, R.P.; Muntenau, M.; Ratziu, V.; Manns, M.; Vogel, A.; Capron, F.; Chedid, A.; Bedossa, P. *J. Hepatol.*, **2003**, *38*, 257.
[97] Clark, J.M.; Brancati, F.L. *Hepatology*, **2004**, *39*, 602.
[98] Avenell, A.; Broom, J.; Brown, T.J.; Poobalan, A.; Aucott, L.; Stearns, S.C.; Smith, W.C.; Jung, R.T.; Campbell, M.K.; Grant, A.M. *Health Technol. Assess.*, **2004**, *8*, 3.
[99] National Institutes of Health *Obes. Res.*, **1998**, *6 (Suppl 2)*, 51S.
[100] Ratziu, V.; Poynard, T. *Hepatology*, **2006**, *44*, 802.

Received: 12 October, 2007 **Revised: 19 January, 2008** **Accepted: 20 January, 2008**