ALCOHOL DEPENDENCE AND ALCOHOLIC LIVER DISEASE

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MEETING SUMMARY

Alcohol dependence is a disabling condition that has a high prevalence, but in Europe only a small fraction of the people diagnosed with alcohol abuse and dependence are treated, representing the widest treatment gap, as compared with other mental disorders. Early diagnosis and monitoring of alcoholic liver disease (ALD) is still insufficiently solved. Although ALD is the most common cause for liver disease in the Western world, it largely remains underestimated and underdiagnosed for many reasons. The recent introduction of non-invasive elastographic techniques such as transient elastography (TE) has significantly improved the early diagnosis of alcoholic liver cirrhosis (ALC). As demonstrated in the literature, inflammation-associated liver stiffness (LS) rapidly decreases during alcohol detoxification, and is also directly correlated to change in LS in both abstinent and relapsing patients. Newly published data show that LS could be used to monitor and validate hepatoprotective effects during nalmefene usage.

Nalmefene is an opioid system modulator that diminishes the reinforcing effects of alcohol, helping the patient to reduce drinking. Three randomised, multicentre, double-blind, placebo-controlled, parallel-group Phase III studies were designed to assess the efficacy and safety of nalmefene in reducing alcohol consumption. Patients with a high or very high drinking risk level (DRL) at baseline and randomisation show a clinically significant effect from nalmefene treatment, which is generally well tolerated. Moreover, reduced alcohol consumption supported by nalmefene in combination with psychosocial support may indeed help to reduce the alcohol-related burden and the large treatment gap.

Nalmefene – A New Treatment Option in Alcohol Dependence

Professor Karl Mann

Alcohol consumption demographics and management of alcohol dependence

Alcohol dependence is a disabling condition that has a high prevalence, with Europe having the highest per capita (10 to over 12.50 litres) pure alcohol consumption of all world regions.[1] Alcohol consumption and dependence can have multiple negative social consequences, such as disrupted relationships with family and friends, violence, crime and accidents, and lack of productivity in the workplace, often leading to unemployment.[1-4] In Europe, only a small fraction (8.3%) of the people diagnosed with alcohol abuse and dependence are treated, representing the widest treatment gap, as compared with other

mental disorders.[5] In a survey conducted from 2009 to 2012, the main reasons given for not receiving alcohol treatment in the past year by American individuals aged 12 and older (n=67,500) who needed treatment and who perceived a need for it were that they were not ready to stop alcohol use (49.5%) and that they had no health coverage and could not afford the costs related to alcohol treatment (30.3%).[6]

While treatment for alcohol use disorder comprises total abstinence using psychotherapeutic and pharmacological treatment modalities, these results show that many individuals are not able or willing to achieve abstinence, resulting in a medical condition that is under-treated.

This is reflected in the latest guidelines from the European Medicines Agency (EMA, 2010), the US National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2007), the Canadian Centre for Addiction and Mental Health (2012), and the British National Institute for Health and Clinical Excellence (NICE, 2011), that highlight that alcohol consumption reduction is an appropriate treatment goal for certain patients.[7-11] Therefore, novel pharmaceutical agents such as nalmefene, which aim to provide support in the reduction of alcohol consumption, represent a significant improvement in the therapeutic armamentarium.

Nalmefene

Adaptation of the brain to alcohol through brain chemistry and neuroadaptive changes leading to dependence has already been established. One of the affected areas of the brain is the mesolimbic dopamine system, a network of interconnected brain regions that includes the ventral tegmental area, the prefrontal cortex, and the nucleus accumbens.[12] Nalmefene (Selincro®, H. Lundbeck A/S) is an opioid system modulator, with antagonist activity at the μ and δ opioid receptors and partial agonist activity at the κ opioid receptor. It diminishes the reinforcing effects of alcohol, helping the patient to reduce drinking.[13,14] The pharmacological properties of nalmefene enable an 'as needed' dosing: it is rapidly absorbed with peak plasma level at 1 hour, with a half-life of approximately 13 hours (longer than that of naltrexone) and high receptor occupancy (87–100%) within 3 hours and also after 26 hours (83–100%).[15] Nalmefene was approved in February 2013 by the EMA for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high DRL, without physical withdrawal symptoms and who do not require immediate detoxification. Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.

Phase III studies on nalmefene

Three randomised, multicentre, double-blind, placebo-controlled, parallel-group Phase III studies were designed to assess the efficacy and safety of nalmefene in reducing alcohol consumption. This Phase III programme enrolled about 2,000 patients with alcohol dependence (Table 1). Two studies comprised a 24-week treatment period followed by a 4-week run-out phase (ESENSE 1 & 2) while the third one (SENSE) was a 52-week study.

Table 1: Main characteristics and results for ESENSE 1, ESENSE 2, and SENSE Phase III studies.

Study name	ESENSE 1 (12014A)	ESENSE 2 (12023A)	SENSE (12013A)
Study duration	24 weeks plus 4-week run-out	24 weeks plus 4-week run-out	52 weeks
Patients enrolled	604 (306 NMF+298 PBO)	718 (358 NMF+360 PBO)	675 (509 NMF+166 PBO)
Difference to placebo at 6 months			
HDDs per month	-2.3 (95% CI, -3.8 to -0.8; p=0.0021)	-1.7 (95% CI, -3.1 to -0.4; p=0.012)	-0.9 (95% CI, -2.1 to 0.4; p=0.160)
TAC (g/day)	-11.0 (95% CI, -16.8 to -5.1; p=0.0003)	-5.0 (95% CI, -10.6 to 0.7; p=0.088)	-3.5 (95% CI, -9.2 to -2.2; p=0.232)

CI: confidence interval; HDD: heavy drinking day; NMF: nalmefene; PBO: placebo; TAC: total alcohol consumption.

Objectives, design, and main endpoints

The ESENSE 1 and 2 studies aimed to evaluate the effect of nalmefene on alcohol consumption at study end.[16,17] The SENSE study[18] aimed to evaluate the safety and tolerability of nalmefene at study end, as well as the effect of nalmefene on alcohol consumption at 6 months. In all three studies, eligible patients were aged 18 or older and were diagnosed with alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).[19] Exclusion criteria related to alcohol consumption comprised DRLs (EMA/World Health Organization [WHO] criteria) below medium (total alcohol consumption [TAC] <40 g/day in men, <20 g/day in women) at baseline,[20,21] 5 or fewer heavy drinking days (HDD; 60 g/day or more of pure alcohol in men, 40 g/day or more in women) in the 4 weeks prior to screening. Other exclusion criteria were aspartate aminotransferase (S-ASAT) and/or alanine transaminase (S-ALAT) levels >3 times upper the normal limits, psychiatric comorbidities, and a Revised Clinical Institute Withdrawal Assessment for Alcohol score of 10 or higher.

Nalmefene 20 mg nalmefene hydrochloride (~18 mg base) tablets were investigated in an 'as-needed' regimen against placebo tablets. One tablet was to be taken on days where patients anticipated a risk of drinking (preferably 1–2 hours prior to anticipated time of drinking), or if the patient had started drinking, as soon as possible thereafter. Treatment could be used daily when patients felt a risk of drinking every day, but for no more than one tablet per day.

In the ESENSE studies, the first visit (V1) was the starting point of an assessment period of 1-2 weeks, leading to 1:1 randomisation at the second visit (V2) to active treatment (nalmefene) or to placebo for 24 weeks, in combination with motivational and compliance intervention.[16,17] Visits to conduct assessments of efficacy and safety were scheduled at weeks 1, 2, and 4, then on a monthly basis (up to V10). In the subsequent 4-week run-out phase, following re-randomisation patients from the active treatment arm either remained on nalmefene therapy or switched to placebo, while patients from the placebo arm remained on placebo. Following completion of this phase, patients where followed up during a 4-week safety follow-up period.

In the SENSE study, the first visit (V1) was followed by an assessment period of 1-2 weeks, then by 3:1 randomisation (at V2) to a 52-week treatment phase with either 'as-needed' nalmefene 18 mg (base) or placebo.[18,22] Visits to conduct assessments of efficacy and safety were scheduled at weeks 1, 2, and 4, then on a monthly basis. Main endpoints in all three studies were the numbers and change from baseline with respect to monthly number of HDDs, monthly TAC, and WHO DRLs.[20,21]

Main clinical findings

Differences to placebo at 6 months in HDDs were of -2.3, -1.7, and -0.9 HDDs per month in the ESENSE 1 ($p<0.05$), ESENSE 2 ($p<0.05$), and SENSE studies, respectively (Table 1).[16-18,22] Differences to placebo at 6 months in terms of TAC were of -11.0, -5.0, and -3.5 g per day in the ESENSE 1, ESENSE 2, and SENSE studies, respectively. A reduction in alcohol consumption during the assessment period prior to randomisation is a known phenomenon.[23,24] In the nalmefene studies 18% (ESENSE 1), 33% (ESENSE 2), and 39% (SENSE) of patients reduced their alcohol consumption in the period between screening and randomisation.[16-18] Comparable patterns were seen for both HDDs and TAC across all three studies.

The benefit of nalmefene was further studied in a pooled 6-month sample from both ESENSE studies.[22] Subgroup analyses showed that patients with high or very high DRL at baseline and randomisation, with no reduction in alcohol consumption prior to randomisation, were associated with the most pronounced clinical benefits of treatment than the general population of the studies (HDD −3.2/months versus −2.0/months, respectively; reduction in TAC, -14.3 g/day versus −7.6 g/day, respectively). Responder analyses in this subgroup showed a 2-category downward shift in WHO DRL (very high-risk to medium-risk consumption; high-risk to low-risk consumption; overall ratio [OR] for 2-category downward shift, 1.87, 95% confidence interval, 1.35-2.59).[25] Similarly, patients with at least high DRL at baseline and at randomisation in the SENSE study (placebo n=42; nalmefene n=141) identified as most likely to benefit ('target population'), the net treatment effect over placebo in terms of reduction of alcohol consumption was more pronounced at 13 months as compared with the total population (HDD −3.6/month versus −1.6/month, respectively; reduction in TAC, −17.3 g/day versus −6.5g/day, respectively).[18] In the pooled 6-month high DRL sample from the ESENSE studies, adjusted mean change from baseline in Impression-Severity of Illness

and Improvement scales (CGI-S and CGI-I) in the nalmefene group were significant versus placebo at 24 weeks.[26]

These results were consistent with liver function test outcomes for the same sample of patients with high DRLs, as glutamyltransferase (GGT) and alanine aminotransferase (ALT) levels at 24 weeks were significantly reduced versus placebo in almost all outcomes (adjusted geometric means, $p<0.05$ for GGT/ALT in ESENSE 1, $p<0.05$ for ALT in ESENSE 2, $p=0.244$ for GGT in ESENSE 2). Safety results from a pooled analysis of all three Phase III studies showed that the most frequent (>10% of patients) adverse events (AEs) in the nalmefene arm (n=1,144) were nausea, dizziness, insomnia, and headache. Overall AEs were of mild or moderate intensity.[16,17,25,27,28] As previously demonstrated by Rehm et al.,[29,30] alcohol consumption reduction of 36 g/day from a baseline of 96 g/day corresponds to a reduced lifetime mortality risk of 119 per 10,000, while a reduction of 36 g/day (3 drinks) from a baseline of 60 g/day corresponds to a reduced lifetime mortality risk of 38 per 10,000.

In conclusion, there remains a large treatment gap for alcohol dependence, but the reduced risks associated with reduced alcohol consumption supported by nalmefene, in combination with psychosocial support are meaningful. Patients with a high or very high DRL at baseline and randomisation showed a greater benefit from nalmefene treatment, which was generally well tolerated.

Non-Invasive Assessments for Early Diagnosis of ALD

Professor Sebastian Mueller

As stated above, nalmefene lowers alcohol consumption in patients addicted to alcohol. But nalmefene also significantly reduces transaminase levels. Indeed, in a pooled analysis from the ESENSE 1 and 2 studies, adjusted geometric means at 24 months were significantly lower in the nalmefene arms (n=187) than in the placebo arms (n=220 for GGT; n=218 for ALT), with respect to γ-GGT (43.5 IU/l versus 53.0 IU/l; $p=0.0005$) and ALT (26.0 IU/l versus 30.7 IU/l; $p=0.0001$) levels.[22,25,26] Whether these effects are related to decreased alcohol consumption or additional pharmacological mechanisms, and whether they can prevent disease progression towards cirrhosis remains largely unknown. For many practical and technical reasons, it is difficult to objectify the hepatoprotective effects of nalmefene treatment in patients with ALD. In addition, early diagnosis and monitoring of ALD is still insufficiently solved. Although ALD is the most common liver disease in the Western world, it largely remains underestimated and underdiagnosed for many reasons: it is under-reported by patients, and underestimated by physicians and by healthcare statistics.[31,32]

Establishing a definite diagnosis is crucial to the subsequent management of the disease, particularly the prevention of complications such as bleeding, ascites, peritonitis, and encephalopathy. If left untreated, ALD naturally progresses to alcoholic steatohepatitis (ASH), either leading to liver cirrhosis and hepatocellular carcinoma (HCC), or to alcoholic hepatitis. As these conditions are associated to a significant risk of mortality, early diagnosis and management of ALD need to be upheld. The diagnosis of ALD and alcoholic cirrhosis usually relies on a combination of clinical, laboratory (GGT, glutamate oxaloacetate transaminase [GOT], ferritin, bilirubin, platelets etc.) and imaging findings (ultrasound, computed tomography, and magnetic resonance imaging).[33,34] However, standard screening tools for ALD can overlook as much as 40% of manifest ALC.[32] Liver biopsy can add useful information in patients with ALD especially the exclusion of comorbidities. However, it is an invasive procedure that is associated with mild and severe complications and shows a rather high sampling error of up to 30%. Liver biopsy is therefore not suitable to follow-up patients with ALD. LS has emerged in the last decade as an important non-invasive parameter to assess the degree of fibrosis, thus monitoring and screening ALD patients at high risk to rapidly progress to cirrhosis. The recent introduction of non-invasive elastographic techniques such as TE (Fibroscan), acoustic radiation force impulse imaging, magnetic resonance elastography, or shear wave elastography has significantly improved the early diagnosis of alcoholic cirrhosis.[35]

LS below 6 kPa is considered as normal, while METAVIR F3 and F4 stage of fibrosis (cirrhosis) have established cut-offs for LS of 8 and 12.5 kPa. Several publications revealed that the diagnostic stiffness cut-offs for cirrhosis stage F4 in ALD patients was higher than that of hepatitis C virus patients. Applying the cut-offs of HCV to ALD patients would yield a very high sensitivity but a lower specificity for ALD.[36-38] These techniques

are of particular importance as they contrast significantly with the level of sample error seen with histological assessments (approximately 30%).[39-43] Indeed, the sample error for LS assessment is of about 3%.[44] Moreover, LS as measured by Fibroscan showed an excellent correlation with histological fibrosis stages in alcoholic patients, and exhibited good diagnostic performance warranting systematic use.[36-38,45-47] However, LS can be influenced by multiple factors: fibrosis, inflammation, cholestasis, liver congestion, or venous pressure.[48-51] Inflammation-increased LS could hinder the detection of fibrosis in ALD patients.[52] Moreover, there remains a 'grey area' between 6 and 8 kPa in which diagnosis is difficult to establish. As demonstrated in the literature, inflammation-associated LS rapidly decreases during alcohol detoxification,[38,53] and is also directly correlated to change in LS in both abstinent and relapsing patients.[54]

In 2013, Mueller et al.[55] proposed an algorithm (Figure 1[33,55]) to either exclude or determine fibrosis stage via LS, recommending that all patients with >6 kPa in LS be assessed according to GOT levels. If the latter are of >100 IU/l, then accurate determination of fibrosis stage is not possible and alcohol detoxification is required before a proper evaluation can be conducted. In patients with GOT levels >100 IU/l, F1-2 fibrosis is established for stiffness ranging from 6-8 kPa, then F3 (>8kPa) and F4 (>12.5 kPa) cut-offs as stated above. Recently, a large multicentre study on >2,000 patients with ALD and chronic hepatitis C was conducted to establish a correlation between GOT levels and LS and to establish optimised, GOT-adapted cut-off values.[56] Among the parameters for liver damage, GOT levels were identified to show the most significant association with LS. Consequently, GOT-adapted cut-off values have been proposed for immediate fibrosis stage assessment or for those patients who will not undergo alcohol withdrawal. In conclusion, it appears that novel non-invasive parameter could be used to monitor hepatoprotective effects during nalmefene usage. In patients with ALD, LS reflects both the degree of inflammation, liver damage, and fibrosis. Novel technologies such as TE show a small sampling error and could allow a better validation of hepatoprotective effects of drugs such as nalmefene.

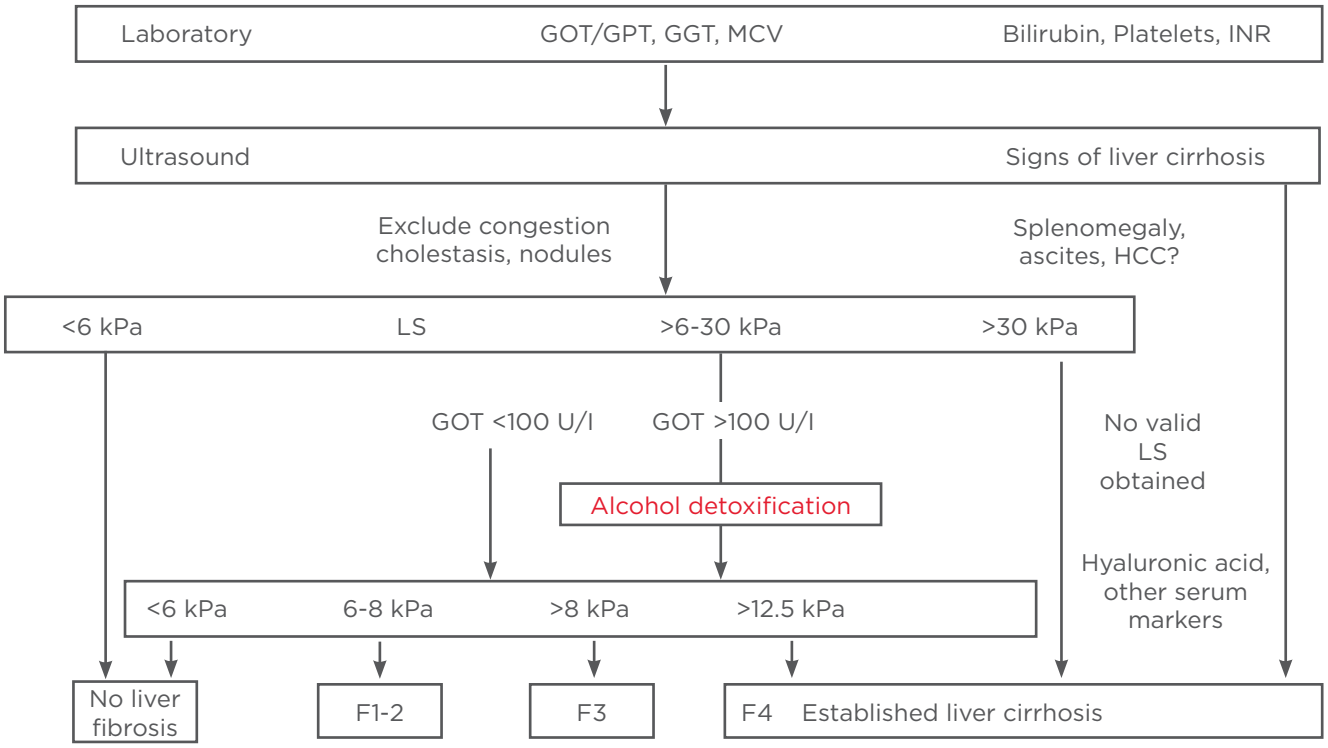

Figure 1: Decision algorithm for fibrosis assessment in alcoholic liver disease.[33,55]
GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; GGT: glutamyltransferase; MCV: mean corpuscular volume; INR: international normalised ratio; HCC: hepatocellular carcinoma; LS: liver stiffness.

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