HHS Public Access

Author manuscript

Addict Behav. Author manuscript; available in PMC 2016 August 06.

Published in final edited form as:

Addict Behav. 2012 April ; 37(4): 561–564. doi:10.1016/j.addbeh.2011.12.010.

Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with hepatitis C virus (HCV) infection

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Abstract

Hepatitis C virus (HCV) and alcoholic liver disease (ALD), either alone or in combination, count for more than two thirds of all liver diseases in the Western world. There is no safe level of drinking in HCV-infected patients and the most effective goal for these patients is total abstinence. Baclofen, a $GABA_B$ receptor agonist, represents a promising pharmacotherapy for alcohol dependence (AD). Previously, we performed a randomized clinical trial (RCT), which demonstrated the safety and efficacy of baclofen in patients affected by AD and cirrhosis. The goal of this post-hoc analysis was to explore baclofen's effect in a subgroup of alcohol-dependent HCV-infected cirrhotic patients. Any patient with HCV infection was selected for this analysis. Among the 84 subjects randomized in the main trial, 24 alcohol-dependent cirrhotic patients had a HCV infection; 12 received baclofen 10mg t.i.d. and 12 received placebo for 12-weeks. With respect to the placebo group (3/12, 25.0%), a significantly higher number of patients who achieved and maintained total alcohol abstinence was found in the baclofen group (10/12, 83.3%; p=0.0123). Furthermore, in the baclofen group, compared to placebo, there was a significantly higher increase in albumin values from baseline (p=0.0132) and a trend toward a significant reduction in INR levels from baseline (p=0.0716). In conclusion, baclofen was safe and significantly more effective than placebo in promoting alcohol abstinence, and improving some LFTs (i.e. albumin, INR) in alcohol-dependent HCV-infected cirrhotic patients. Baclofen may represent a clinically relevant alcohol pharmacotherapy for these patients.

Keywords

alcohol dependence; alcoholic liver disease; Hepatitis C virus; cirrhosis; alcohol pharmacotherapy; baclofen

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1. Introduction

Alcohol represents one of the most common causes of liver cirrhosis in the Western world. Furthermore, alcohol dependence (AD) represents an independent risk factor for hepatitis C virus (HCV) infection (Mendenhall et al., 1993; Rosman et al., 1996) and the prevalence of HCV is 3- to 30-fold higher in alcoholic individuals compared with the general population (Singal and Anand, 2007). HCV and alcoholic liver disease (ALD), either alone or in combination, count for more than two thirds of all liver diseases in the Western world (Mueller et al, 2009). Alcohol consumption accelerates HCV-related liver disease and the co-existence of both alcohol consumption and HCV result in a synergistic effect (but see: Anand and Thornby, 2005). For example, consumption of 50g/day of alcohol increased the rate at which fibrosis progresses in HCV-infected individuals (Poynard et al., 1997), and the risk factor for developing cirrhosis was significantly higher in HCV-infected patients that abused alcohol, compared to those who did not consume alcohol (Corrao and Arico', 1998). Indeed, even moderate alcohol consumption may turn into progressive liver fibrosis (Westin et al., 2002). Therefore, there is no safe level of drinking in HCV-infected patients and the most effective goal for these patients is to achieve total alcohol abstinence (Mueller et al., 2009).

Pharmacotherapies represent important therapeutic tools in AD (Leggio et al, 2010a), but randomized clinical trials (RCTs) with alcohol pharmacotherapies typically exclude patients with significant liver diseases because of extensive liver metabolism of some of these drugs and/or the risk of drug-related hepatotoxicity. Indeed, both disulfiram and naltrexone carry on a risk for hepatotoxicity, especially if administered to patients with liver diseases (Chick, 1999; Mosby's Drug Consult, 2005). Baclofen, a $GABA_B$ receptor agonist, represents a promising novel alcohol pharmacotherapy (Leggio et al., 2010b). Consistent with preclinical studies (reviewed in: Maccioni and Colombo, 2009), the majority of the clinical studies suggest baclofen's efficacy in AD (Addolorato et al., 2000, 2002, 2006, 2011; Flannery et al., 2004; Leggio et al., 2008a,b; but see: Garbutt et al, 2010). Indeed, our group performed a RCT with baclofen in patients affected by AD and cirrhosis, which demonstrated the safety and efficacy of baclofen in this specific population (Addolorato et al., 2007). Compared to placebo, more patients assigned baclofen achieved and maintained alcohol abstinence throughout the study. Also, individuals treated with baclofen, compared to placebo, had significantly greater improvement in biomarkers of liver injury, i.e. alanine aminotransferase (ALT), aspartate transaminase (AST), and in liver function tests (LFTs), i.e. albumin, international normalized ratio (INR) and bilirubin.

The goal of the present post-hoc analysis was to explore if baclofen's effect was still present in a subgroup of alcohol-dependent HCV-infected cirrhotic patients, and if there were differences in baclofen's safety and response among HCV-infected and HCV-negative patients.

2. Methods

2.1. Brief Overview of the Main RCT

For a detailed description of the main trial, see Addolorato et al. (2007). Briefly, inclusion criteria included age range of 18-75 years, and diagnoses of AD and cirrhosis. Exclusion criteria included, among the others, medical and/or psychiatric contraindications to take baclofen. Notably, the presence of HCV infection was not exclusion. Eighty-four patients were randomized to receive either placebo or baclofen 10mg t.i.d. for 12 weeks. Patients were seen each week for the first month, and then every other week. At each visit, psychological counselling was also provided. The study was conducted at the Alcohol Treatment Unit, Catholic University of Rome (Italy), it was approved by the local Ethics Committee and registered in ClinicalTrials.gov (NCT00525252).

2.2. Patients and Methods

Out of the 84 patients enrolled in the main RCT (Addolorato et al., 2007), any patient with HCV infection was selected for this post-hoc analysis. The goal of this analysis was to explore the effects of baclofen, as compared to placebo, on total alcohol abstinence, and on ALT, AST and LFTs in alcohol-dependent HCV-infected cirrhotic patients. An additional goal was to compare the HCV-infected subgroup with the rest of the sample (i.e. HCV-negative) to investigate possible differences between the two groups in terms of safety and response to baclofen.

2.3 Statistical Analysis

All discrete variable were reported as percentage and compared between the two treatment groups or in HCV-infected and negative group with the Fisher's exact test. The continuous variables were expressed as median and corresponding interquartile range and compared by means of U-Mann Whitney test. All analyses were carried out with SAS software, version 9.1. For all tested hypotheses, two-tailed p-values less than 0.05 were considered to be significant.

3. Results

3.1. Demographics and baseline characteristics of the HCV-infected sub-group

Among the 84 subjects randomized in the main trial, 24 (29%) alcohol-dependent cirrhotic patients had a HCV infection. Out of these 24 alcohol-dependent HCV-infected cirrhotic patients, 12 received baclofen 10mg t.i.d. and 12 received placebo for 12-weeks. The baseline characteristics of the HCV-infected sub-group are outlined in the Table 1. No significant difference was found in the number of drop-outs between baclofen and placebo groups [2 out of 12 patients (16.7%) vs. 3 out of 12 patients (25.0%) respectively; p=1.000, Fisher's exact test].

3.2. Differences at baseline between HCV-infected and HCV-negative patients

A comparison of the HCV-infected vs. HCV-negative patients showed no differences in all baseline demographics characteristics and blood tests, with the exception of significantly

higher baseline ALT (p=0.0095) and AST (p=0.0192) levels in the HCV-infected than in the HCV-negative patients.

3.3. Effects of Baclofen on Alcohol and Liver Outcomes in alcohol-dependent HCV-infected cirrhotic patients

As displayed in Figure 1, with respect to the placebo group (3 out of 12, 25.0%), a significantly higher number of patients who achieved and maintained total alcohol abstinence was found in the baclofen group (10 out of 12, 83.3%; p=0.0123, Fisher's exact test). When considering only subjects who completed the study the statistic was still significant (p=0.0055).

Treatment with baclofen resulted in a clinical improvement in LFTs, i.e. in the baclofen group, compared to placebo, there was a significantly higher increase in albumin values from baseline (p=0.0132) and a trend toward a significant reduction in INR levels from baseline (p=0.0716). No significant difference in AST, ALT, GGT, MCV and creatinine values was found between baclofen and placebo group (p>0.05).

Finally, as in the main trial, no clinically significant side-effects were reported, and no patient discontinued the drug. The side-effects were vertigo (1 patient), tiredness (1 patient), sleepiness (1 patient), headache (1 patient), in the baclofen group and headache (3 patients), fatigue (1 patient) and vertigo (1 patient) in the placebo group.

4. Discussion

This analysis demonstrates that baclofen was significantly more effective than placebo in promoting alcohol abstinence, and improving some LFTs (i.e. albumin, INR) in alcohol-dependent HCV-infected cirrhotic patients. Though a very small sample, the most relevant finding of this study is that baclofen demonstrated its efficacy and safety in promoting total alcohol abstinence in this subgroup of patients. The co-existence of alcohol and HCV, as compared to either condition alone, dramatically increases the risk of developing severe liver diseases, i.e. fibrosis, cirrhosis and hepatocellular carcinoma. Not only is heavy drinking deleterious for the liver in HCV-infected patients, but also moderate alcohol consumption may aggravate liver disease in HCV-infected patients (Westin et al., 2002). As a matter of fact, the National Institute for Alcohol Abuse and Alcoholism (NIAAA; see NIAAA webite) highlights that even ‘light-to-moderate’ drinking (≥2 drinks/day for males; ≥1 drinks/day for females) may be “too much” in some conditions, including HCV infection.

As there are no safe levels of alcohol consumption in HCV-infected individuals, total alcohol abstinence represents a very important goal to achieve for alcohol-dependent HCV-infected patients. Pharmacotherapies, in conjunction with psychological approaches, may represent effective tools for clinicians. This study shows that while all patients received psychological counseling during the study, adding baclofen resulted in a significant improvement in alcohol abstinence. Therefore, this study suggests baclofen may represent a clinically relevant alcohol pharmacotherapy for these patients, a feature of particular importance if we consider that alcohol pharmacotherapy trials typically exclude patients with clinically significant liver diseases.

Though a small sample (n = 24), our study demonstrated that treatment with baclofen, compared to placebo, resulted in a significant improvement in some LFTs (albumin and INR). Notably, the impairment of these parameters represents a very important factor for clinically relevant complications, such as ascites (albumin) and bleeding (INR).

Consistent with the main trial (Addolorato et al., 2007), this analysis showed the safety of baclofen, when administered to alcohol-dependent HCV-infected cirrhotic patients, including the complete lack of hepatic or renal side-effects. Baclofen is mainly excreted unmodified by the kidney (Davidoff, 1985), therefore possible changes in the renal function in baclofen-treated patients would be an important concern. In this study, no subjects experienced increased creatinine levels, nor were differences found in creatinine levels between the two groups. This was expected given the exclusion criteria (i.e. any kidney disease, including hepato-renal syndrome), and the lack of renal side-effects in the whole sample (Addolorato et al., 2007). Nevertheless, given that in addition to the liver, HCV may lead to extra-hepatic manifestations, including the kidney (e.g. membranoproliferative glomerulonephritis associated with Type 2 cryoglobulinemia) (Kamar et al, 2008), this study still provides important safety information, i.e. the lack of changes in renal function in alcohol-dependent HCV-infected cirrhotic patients treated with baclofen.

In the parent study, we found a significant improvement in ALT (and LFTs) in baclofen-treated patients (Addolorato et al., 2007). Here, it is highly likely that the presence of HCV infection was responsible for the significantly higher baseline ALT and AST levels, as compared to the HCV-negative patients, and for the lack of a significant improvement in ALT levels in the baclofen group (in spite of a significant improvement in two clinically important LFTs, i.e. albumin and INR). It is possible that longer treatment with baclofen might reveal an improvement in markers of liver injury (i.e. ALT, AST) in this sub-group, therefore longer prospective studies will be required to address this.

Certainly the improvement in LFTs in the baclofen group was due to the ability of baclofen to stop alcohol drinking. Therefore, when AD and HCV infection co-exist, ideally the best approach will be to combine a safe alcohol pharmacotherapy (e.g. baclofen) that promotes abstinence and improve liver function (i.e. LFTs), together with antiviral therapies that reduce the viral load and improve hepatic injury (i.e. ALT). As such, future studies may consider combining baclofen and antiviral therapies, and/or using baclofen as an alcohol treatment ‘bridge’ before starting HCV therapies. In fact, heavy alcohol consumption represents a relative contraindication for antiviral therapies (Soriano et al., 2007). However, with appropriate treatment, coinfected people deemed at first ineligible for HCV therapy can become eligible (Adeyemi et al., 2004; Mehta et al., 2005). Therefore, baclofen may play an important role as an alcohol treatment in the context of antiviral HCV therapies, and this is an even more important goal to pursue if we consider the recent approval of new antiviral therapies.

These data also suggest that an additional area to explore will be the potential for baclofen to be used for alcohol-dependent HCV-infected cirrhotic patients (the same kind of population analyzed here) who need orthotopic liver transplantation (OLT), but for which current alcohol consumption represents a contraindication (see: Burra and Lucey, 2005). Addressing

alcohol consumption in alcohol-dependent HCV-infected cirrhotic patients who need an OLT is particularly important, given that these patients are more likely to die on the waiting list than those with either ALD or HCV alone, but after transplantation, non-risk adjusted graft and survival of alcohol-dependent HCV-infected patients are comparable to those of patients with HCV or ALD alone (Carbone & Neuberger, 2010).

The present analysis has some significant limitations, i.e. the post-hoc kind of analysis, the very small sample, and the lack of additional data on HCV (i.e. genotype and HCV-RNA). Nonetheless, this study provides significant preliminary information, which suggests the need to perform a large prospective RCT with baclofen to treat AD in HCV-infected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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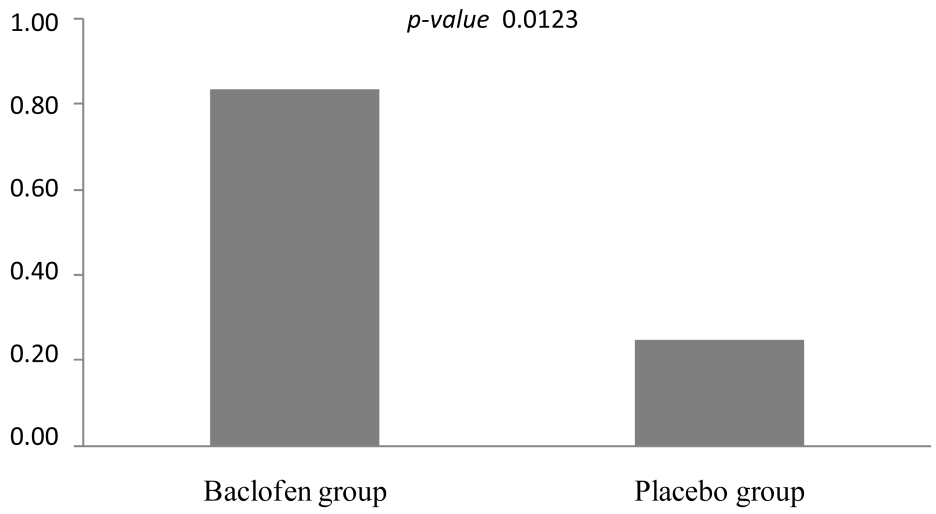

Figure 1.

Figure 1 shows that, with respect to the placebo group (3 out of 12, 25.0%), a significantly higher number of alcohol-dependent HCV-infected cirrhotic patients achieved and maintained total alcohol abstinence in the baclofen group (10 out of 12, 83.3%; p=0.0123, Fisher's exact test).

Table 1

Demographic and addiction characteristics of the sub-group of alcohol-dependent cirrhotic patients with HCV infection (n = 24).

	Baclofen group (n = 12)	Placebo group (n= 12)	P-value
Median of Age (Interquartile range)	47.0 (43.0-60.0)	53.5 (44.0-60.0)	0.6295
Male n (%)	10 (83.3%)	7 (58.3%)	0.3707
Married n (%)	8 (66.7%)	8 (66.7%)	1.000
Education > 13 years n (%)	2 (16.7%)	6 (50.0%)	0.1930
Employed n (%)	8 (66.7%)	11 (91.7%)	0.3168
Median of daily consumption (drinks) of alcohol in years (Interquartile range)	16.0 (12.0-28.0)	21.0 (13.0-24.5)	0.9447
Median of duration of alcohol addiction in years (Interquartile range)	19.0 (16.5-23.5)	20.5(17.5-29.0)	0.5214