Combination Treatment in Non-alcoholic Fatty Liver Disease—Beginning of a New Era

Torres DM, Jones FJ, Shaw JC, Williams CD, Ward JA, Harrison SA. Rosiglitazone versus rosiglitazone and metformin versus rosiglitazone and losartan in the treatment of non-alcoholic steatohepatitis in humans: A 12-month randomized, prospective, open-label trial. *Hepatology* 2011;54:1631–9.

Abstract

Medication combinations that improve the efficacy of thiazolidinediones or ameliorate weight-gain side effects of the therapy represent an attractive potential treatment for non-alcoholic steatohepatitis (NASH). The aim of this randomized, open-label trial was to assess the efficacy of rosiglitazone and metformin in combination versus rosiglitazone and losartan, compared with rosiglitazone alone, after 48 weeks of therapy. A total of 137 subjects with biopsy-proven NASH were enrolled and randomly assigned to receive either 4 mg twice daily of rosiglitazone, 4 mg of rosiglitazone and 500 mg of metformin twice daily, or 4 mg of rosiglitazone twice daily and 50 mg of losartan once daily for 48 weeks. Patients were screened for other etiologies of chronic liver disease, including the daily alcohol intake in excess of 20 g. Repeat liver biopsy was performed after 48 weeks of therapy and reviewed in a blinded fashion by a single expert hepatopathologist. The primary aim of this study was to assess for the differences between treatment groups in the improvement of steatosis, hepatocellular inflammation, and fibrosis. In total, 108 subjects completed the trial. Primary outcome revealed no significant difference between treatment groups in all histologic parameters (steatosis, $P=0.137$; hepatocellular inflammation, $P=0.320$; fibrosis, $P=0.229$). Overall improvement in steatosis, hepatocellular inflammation, ballooning degeneration, and

fibrosis was observed ($P\leq 0.001$). Serum aminotransferases were reduced in all three groups ($P<0.001$ within treatment, $P>0.05$ between groups). Metformin did not significantly mitigate weight gain ($P=0.051$). **Conclusion:** Forty-eight weeks of combination therapy with rosiglitazone and metformin or rosiglitazone and losartan confers no greater benefit than with rosiglitazone alone with respect to histopathology.

Comment

Non-alcoholic fatty liver disease (NAFLD) is a spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), which has the propensity to progress on to cirrhosis and hepatocellular carcinoma. Treatment of NAFLD is still evolving, and no single agent is effective in curing these patients. Lifestyle modifications and sustained weight loss have been shown to be effective in the treatment of patients with NAFLD but is difficult to achieve and sustain.¹ The focus of pharmacological agents has been on improving the insulin resistance and oxidative stress, two important pathways in the pathogenesis of NAFLD. Insulin sensitizers such as thiazolidinediones (rosiglitazone and pioglitazone) have been found to be effective in improving the NAFLD histology (predominantly steatosis and inflammation) with little effect on hepatic fibrosis.¹ The major problem with the use of glitazones has been weight gain which might counter the beneficial effect of these drugs in patients with NAFLD. Metformin, another insulin-sensitizing drug with anti-tumor necrosis factor (TNF) properties, has also been found to be effective in patients with NAFLD and is usually free of side effects but the histological data showing its efficacy are not robust.¹ Angiotensin II receptors are expressed on hepatic stellate cells and losartan; an angiotensin II receptor blocker has been shown to improve both the necro-inflammation and the hepatic fibrosis both in the experimental model and in patients with NAFLD.¹ There are various other drugs used in the treatment of NAFLD, but overall even with the best of treatment histological improvement cannot be achieved in >40–45% of patients with NAFLD. Thus, there is a need to have better drugs and strategies in the treatment of patients with NAFLD.

Torres et al² in the recent issue of *Hepatology* adopted a new strategy of using the combinations of drugs. They investigated two different combination therapies and randomized 137 subjects with biopsy-proven NASH to a 48-week course of rosiglitazone 4 mg twice daily alone, or in combination with either metformin 500 mg twice daily or losartan 50 mg daily.² The rationale for adding metformin to rosiglitazone was to further improve the insulin

Received: 7.12.2011; Accepted: 11.12.2011

Address for correspondence: Ajay K Duseja, Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

E-mail: ajayduseja@yahoo.co.in

Abbreviations: FDA: Food and Drug Administration; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; TNF: tumor necrosis factor

doi: 10.1016/S0973-6883(11)60242-9

sensitivity and to mitigate the weight gain caused by rosiglitazone. The primary endpoint was the change in hepatic histology as evidenced by at least one point improvement in steatosis, inflammation, and fibrosis. Steatosis, inflammation, and fibrosis improved between baseline and the end of treatment within each treatment arm, but the changes in liver histology were statistically not different between the three treatment groups.² Although not found effective, theirs is practically the first study to use the combination of drugs in the treatment of NAFLD and opens the doors for further studies to look at the efficacy of various combinations in the treatment of NAFLD. Even though the study takes a lead in adopting the new concept, it is limited by few issues including the abrupt termination of the trial by the Food and Drug Administration (FDA) due to severe restrictions on rosiglitazone use in the United States, leading to an underpowered sample size. Perhaps, they also did not choose the best combination for the treatment of NAFLD patients. As suggested in the recent meta-analysis, the best results in patients with NAFLD are seen either with thiazolidinediones or with vitamin E which has anti-oxidant properties.¹ Hence, the best combination would have been one of the glitazone

group of drugs and vitamin E. Secondly, the dose of 1 g/day of metformin used in their patients looks inadequate for the adult patients, and finally the use of losartan as an anti-fibrotic drug and assessing hepatic fibrosis as a primary outcome even when fibrosis was not the prerequisite for inclusion makes things more difficult. If the expected benefit from losartan was to significantly improve fibrosis, then there should have been sufficiently advanced fibrosis to begin with, or if the objective was to reduce the progression of fibrosis, then the study duration should have been longer than 48 weeks.

In spite of the limitations, the study is a welcome step and dawn a new era of combination treatment in patients with NAFLD.

REFERENCES

1. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of non-alcoholic fatty liver disease. *Hepatology* 2010;52:79–104.
2. Torres DM, Jones FJ, Shaw JC, Williams CD, Ward JA, Harrison SA. Rosiglitazone versus rosiglitazone and metformin versus rosiglitazone and losartan in the treatment of non-alcoholic steatohepatitis (NASH): a 12-month-randomized, prospective, open-label trial. *Hepatology* 2011;54:1631–9.

Liver Transplantation in Alcoholic Hepatitis—It's All Time Game

Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* 2011;365:1790–800.

Abstract

Background: A 6-month abstinence from alcohol is usually required before patients with severe alcoholic hepatitis are considered for liver transplantation. Patients whose hepatitis is not responding to medical therapy have a 6-month survival rate of about 30%. Since most alcoholic hepatitis deaths occur within 2 months, early liver transplantation is attractive but controversial. **Methods:** We selected patients from 7 centers for early liver transplantation. The patients had no prior episodes of alcoholic hepatitis and had scores of 0.45 or higher according to the Lille model (which calculates scores ranging from 0 to 1, with a score ≥ 0.45 indicating nonresponse to medical therapy and an increased risk of death in the absence of transplantation) or rapid worsening of liver function despite medical therapy. Selected patients also had supportive family members, no severe coexisting conditions, and a commitment to alcohol abstinence. Survival was compared between patients who

underwent early liver transplantation and matched patients who did not. **Results:** In all, 26 patients with severe alcoholic hepatitis at high risk of death (median Lille score 0.88) were selected and placed on the list for a liver transplant within a median of 13 days after nonresponse to medical therapy. Fewer than 2% of patients admitted for an episode of severe alcoholic hepatitis were selected. The centers used 2.9% of the available grafts for this indication. The cumulative 6-month survival rate ($\pm$ SE) was higher among patients who received early transplantation than among those who did not ($77 \pm 8\%$ vs $23 \pm 8\%$, $P < 0.001$). This benefit of early transplantation was maintained through 2 years of follow-up (hazard ratio, 6.08; $P = 0.004$). Three patients resumed drinking alcohol: one at 720 days, one at 740 days, and one at 1140 days after transplantation. **Conclusion:** Early liver transplantation can improve the survival in patients with a first episode of severe alcoholic hepatitis not responding to medical therapy.

Comment

The decision to perform liver transplantation in patients with alcoholic liver disease (ALD) has always been difficult with the earliest programs even considering this to be a contraindication because of the self-inflicted nature of the illness, risk of recidivism, poor adherence to post-transplant care, and all this in the presence of shortage of livers. Thereafter, liver transplantation is being performed in patients with ALD with a requirement of at least 6 months of

abstinence from alcohol intake and short-term (1- to 7-years) graft and patient survival remain at par with, if not superior to non-ALD patients remaining abstinent. A 2008 meta-analysis of 50 studies looking at the predictors of recidivism found three significant, albeit modest, variables: a poor social support system, a family history of alcohol abuse/dependence, and pretransplant abstinence of 6 months or less.¹ Studies over the years have provided convincing data for and against the 6-month abstinence requirement and this minimal period of abstinence is sometimes waived if the patient is deemed too ill to survive beyond 6 months without a liver transplant. This rationale applies to patients with severe, acute alcoholic hepatitis who have little or no chance of surviving 6 months.

Using the same principle, Mathurin et al² reported their results of a prospective study of liver transplantation in highly selected patients with severe alcoholic hepatitis who were unlikely to survive 6 months. The authors compared the survival in the cohort of transplant patients with that in two matched control groups of patients who were not offered transplantation. The patients were carefully selected at each center; selected patients had good social support, a contract for abstinence, no prior episodes of known ALD, and no evidence of severe psychological disease. This resulted in 26 patients being selected over a period of >4 years, representing <2% of patients admitted for an episode of severe alcoholic hepatitis. The results of transplantation were excellent, with a 6-month survival rate of 77%. The rate of recidivism to alcohol use was low, with only 3 of 26 patients resuming drinking alcohol; of these three, none had graft dysfunction. The rate of survival was superior to that among patients who were not offered transplantation (23% survival at 6 months).²

The study definitely answers the most difficult question about the timing of liver transplantation in sick patients with severe alcoholic hepatitis, but simultaneously also raises some pertinent questions. The most important question being if the same rule of early transplantation could be applied to all patients. No doubt, these patients are very sick and are unlikely to survive without transplant, but is it justified to transplant all such patients with the risk of recidivism (because of the short period of abstinence prior to transplant) and the recurrence of disease. Without a good objective tool to predict the risk of recidivism that can be applied fairly and equally across candidates, there is likely possibility of a bias in the selection of candidates. There may have been bias in the selection of the candidates in this study as well. It would have been useful to look at the overall population of patients with alcoholic hepatitis to determine whether the group that was selected represented the overall population of patients.

The study definitely brings a ray of hope for a group of patients with severe alcoholic hepatitis (not responding to medical treatment) that is emotionally stable and is determined for long-term abstinence with good family support. But these patients need to be carefully differentiated from the group of patients without family support that are emotionally unstable and are likely to go back to alcoholism after liver transplantation.

REFERENCES

1. Dew MA, Di Martini AF, Steel J, et al. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. *Liver Transpl* 2008;14:159–72.
2. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* 2011;365:1790–800.