The Course of Galactose Elimination Capacity in Patients With Alcoholic Cirrhosis: Possible Use As a Surrogate Marker for Death

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There is increasing interest for the use of surrogate end points in the evaluation of treatments in patients with liver disease, but adequate validation is seldom available. This study aimed to describe the different course of galactose elimination capacity in patients with alcoholic cirrhosis who continued to drink or abstained from alcohol consumption during follow-up, and to validate changes in galactose elimination as a surrogate end point for death from liver-related causes. Forty-five patients with alcoholic cirrhosis (22 who continued drinking throughout the study period, and 23 who stopped drinking and were abstinent throughout the study period) were retrospectively selected among patients who had galactose elimination capacity measured at 6-month intervals. During follow-up 10 drinkers and 3 abstainers died of liver-related causes ($P = .025$). Abstainers showed a transient improvement in galactose elimination capacity, followed by a decrease. Continuous drinkers showed a reduction from the beginning. According to Cox's regression analyses, persistent alcohol abuse and galactose elimination capacity were separately related to the risk of death, but, when a time-dependent model was fitted containing galactose elimination capacity and persistent alcohol abuse, only the former remained significant. This implies that variations in the risk of death occurring as a consequence of abstinence from alcohol consumption may be predicted from changes in galactose elimination capacity, and that the mechanisms through which abstinence influences survival are strictly linked to the mechanisms responsible for the changes in the test. Because of the strict association of decrease in galactose elimination capacity and short survival, as proved in several series, this observation represents adherence to the criteria requested for adequacy of a surrogate end point. In conclusion, in alcoholic cirrhosis the decrease in galactose elimination capacity is an adequate surrogate end point for death from liver-related causes, which is worth testing in other conditions and in response to other treatments. (HEPATOLOGY 1996;24:820-823.)

Recent research in clinical epidemiology focused on the validation of surrogate end points to be used instead of the true, clinically relevant events which need a long time to take place.[1,2] Before a surrogate end point may be used in the clinical practice, its adequacy must be proven in the clinical problem, and with the therapeutic options under study.[3] The more stringent method to validate a surrogate end point is the analysis of a trial or a series of trials performed on the clinical problem under study, to verify if (or to what extent) the surrogate end point meets the criteria proposed by Prentice.[4] In particular, the first criterion requests that the occurrence of the surrogate end point is linked to the occurrence of the true end point; the second criterion requests that the mechanism(s) through which treatment influences the true end point is directly and at the same time related to the occurrence of the surrogate end point.

Preliminary data have suggested a possible use of changes in quantitative liver function tests as surrogate markers for survival in patients with chronic liver disease.[5] The first Prentice's criterion is proven by the strict association of decrease in quantitative liver function tests and survival shown in many series.[6-8] The adherence to the second criterion is more difficult to prove, and should be assessed for any single treatment. Unfortunately, in patients with chronic liver disease, the lack of effective treatments improving liver function and survival makes this second criterion difficult to fulfill. Abstinence from alcohol in alcoholic cirrhosis may be considered a model treatment improving survival through improvement in liver function, and the different course of values of a quantitative liver function test in patients who start abstinence, compared with that of patients who continue drinking, may mimic the effect of a drug treatment in a clinical trial. Very few data are available on the course of quantitative liver function tests during follow-up in patients with cirrhosis in relation to persistent alcohol abuse or abstinence.[9]

In the present study we described the course of galactose elimination capacity (GEC) in a group of cirrhotics with alcohol abuse, divided into a group who abstained during follow-up and a group who continued drinking, and analyzed the possible use of decrease in GEC as a possible marker for death in cirrhotics with alcohol abuse, trying to validate the adherence to the second Prentice's criterion.[4] If the improvement in GEC in patients who start abstinence is strictly linked to increased survival, this will be a clue to the possible use of GEC as a surrogate marker for survival in this disease also in relation to different treatments.

PATIENTS AND METHODS

Forty-five patients with cirrhosis and chronic alcohol abuse were retrospectively selected among patients followed with GEC determi-

Abbreviation: GEC, galactose elimination capacity.

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nations at 6-month intervals in the Departments of Clinical Medicine of the Universities of Bologna and Padua, Italy. Patients were included in the analysis if: (1) diagnosis of cirrhosis was histologically proven and patients reported chronic alcohol intake of more than 100 g/d of alcohol for more than 5 years; (2) follow-up visits and interviews with relatives documented either a persistent alcohol abuse or a persistent abstinence from alcohol from the beginning of follow-up to the end of the study period; and (3) baseline GEC value was above 2.5 mg/kg/min, and no other relevant disease was present. Patients were divided into a group of persistent drinkers (22 patients, group A) and a group of persistent abstainers (23 patients, group B). No patient had serological markers of persistent hepatitis B virus infection, but 7 and 9 patients, respectively, were anti-hepatitis C virus positive according to a Radio-Immuno-Blotting-Assay-2 test. Informed consent was obtained from each subject and the study protocol was conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients were followed until death or for up to 4 years, and during this time 202 GEC determinations were performed according to the single injection technique[10] at intervals ranging 5 to 7 months. Tests were always performed after at least 2 days of abstinence, when blood ethanol concentrations were undetectable, to exclude a possible inhibition of galactose elimination caused by ethanol. Mean follow-up was 32 months. Death from liver-related causes was considered the true end point of the study. Therefore, patients who died of non–liver-related causes were censored at the time of death.

The course of GEC in patients who continued drinking or started abstinence was described drawing curves of the mean values at the various follow-up times, separately for patients who died during follow-up and for patients who survived. To evaluate changes of GEC during follow-up according to persistent alcohol abuse and survival, a two-way ANOVA was employed. In addition, the method proposed by Christensen et al.[11] was used to describe the course of GEC. According to this method, developed to avoid the bias because of decreasing the number of patients with time, because part of the patients included late have a shorter follow-up, and part of the patients die during follow-up, the course of GEC was evaluated separately in groups of patients having three or four subsequent observations. Because every patient can contribute to the mean only until he is under observation, patients with the shortest follow-up time only contribute to the shortest interval, whereas patients with the longest follow-up contribute to all intervals. Observing the trend in groups made of the same subjects one may assess the effect of time in patients surviving this interval. Comparing corresponding values in adjacent groups, one can estimate the size and the direction of the selection effect because of the loss of patients during follow-up for any cause, including death. The course in patients with the same number of observations was assessed by one-way ANOVA and paired Student's t test. The selection effect was tested by comparing baseline GEC values in patients with four observations with those of patients with three observations. Unpaired Student's t test was employed. Survival in the two groups was compared by Kaplan-Meier analysis.[12]

To assess the possible value of decrease in GEC as surrogate marker for liver-related death, the method proposed by Lin et al.[13] was used. With this purpose, a series of Cox's regression models[14] were built. First, separate models for alcohol abuse and for decrease in GEC were built considering GEC as a time-dependent variable.[15] Then, changes in significance of alcohol abuse were analyzed when GEC was added as a time-dependent variable to alcohol abuse itself. According to this analysis, if alcohol abuse loses its value as predictor of death when GEC is added, this means that GEC includes most of the prognostic value of alcohol abuse, and that alcohol abuse influences survival through its effect on GEC.

TABLE 1. Clinical and Biochemical Characteristics of Investigated Patients

	Group A (Continuous Drinkers, n = 22)	Group B (Continuous Abstainers, n = 23)
Age (yr)	58 ± 7	56 ± 6
Gender (M/F)	20/2	20/3
Child-Pugh class	8 ± 1	8 ± 2
Anti-HCV+	7	9
GEC (mg/min/kg body weight)	4.56 ± 1.27	4.24 ± 0.96

NOTE. Data given as mean ± SD. No significant difference in any variable according to Student's t test or χ^2 test, when applicable.

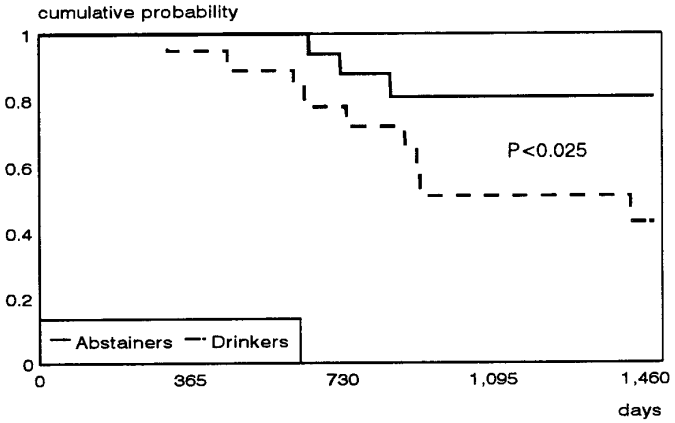

FIG. 1. Kaplan-Meier survival plot of patients who continued drinking (– – –) or who abstained during follow-up (———).

RESULTS

Course of GEC During Follow-Up. The two groups, although not randomized, but retrospectively selected according to predefined criteria, were very similar for general demographic, clinical, and biochemical characteristics (Table 1).

During follow-up, 10 patients in group A and 3 patients in group B died from liver-related causes. Survival was significantly longer in patients of group B according to a Kaplan-Meier analysis (Fig. 1). Three more patients died of conditions unrelated to liver disease.

The course of GEC in the two groups was rather different. Indeed, in continuous drinkers who died during follow-up, there was a progressive decrease in GEC, whereas in continuous drinkers who survived, GEC remained rather stable for the whole study period. In patients who started abstinence there was an initial increase in GEC both in survivors and in those who eventually died. After the first follow-up examination, abstainers who died during follow-up showed a progressive decrease in GEC, whereas survivors had steady values of GEC (Fig. 2). Indeed, according to ANOVA results, decrease in GEC at the first follow-up visit was significantly related to persistent alcohol abuse ($F = 9.74$; $P = .003$), but not to the outcome ($F = .30$; $P = .59$), changes in GEC at the second follow-up visit were significantly related to persistent alcohol abuse ($F = 4.95$; $P = .03$) but more strictly to the outcome ($F = 8.55$; $P = .007$), and changes in GEC at the third follow-up visit were significantly related to the outcome ($F = 8.20$; $P = .01$), whereas persistent alcohol abuse was not a significant factor ($F = 2.18$; $P = .15$). Nevertheless, a significant interaction was observed between persistent alcohol abuse and outcome ($F = 4.74$; $P = .04$), which implies that the decrease in GEC was more evident in patients who persisted in alcohol abuse and died during follow-up.

Analyzing the course in patients with the same number of follow-up visits, the different course in abstainers and in continuous drinkers was more evident (Fig. 3). Indeed, in abstainers there was an evident increase in GEC at the first follow-up visit, and subsequently a progressive decrease in GEC. The shift toward the bottom of the lines with decreasing number of follow-up visits suggests that a selection effect because of the presence of long-term survivors was operating. Indeed, patients with three follow-up visits had significantly lower GEC values than patients with four follow-up visits (t

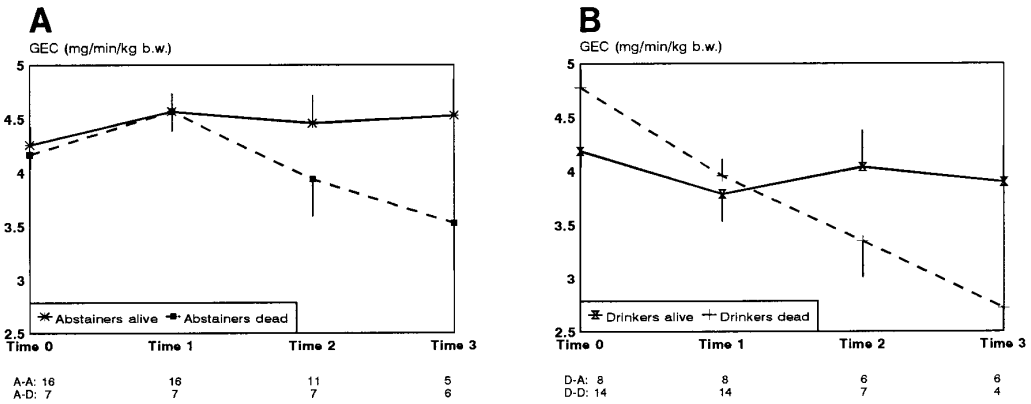

FIG. 2. (A) Course of GEC in abstainers at various follow-up visits, divided into those who survived (A-A; ———) and those who eventually died (A-D; – – –). Vertical bars = standard error of the mean. On the bottom: number of patients at each follow-up visit. (B) Course of GEC in continuous drinkers at various follow-up visits, divided into those who survived (D-A; ———) and those who eventually died (D-D; – – –). Vertical bars = standard error of the mean. On the bottom: number of patients at each follow-up visit.

= 2.29; $P = .04$). In continuous drinkers there was a progressive and very evident decrease in GEC from the first determination; the selection effect because of long-term survivors was not statistically significant.

Assessment of GEC As A Surrogate Marker. Persistent alcohol abuse was significantly related to survival according to Cox's regression analysis. GEC was also significantly related to survival according to a time-dependent Cox's regression analysis (Table 2). When a Cox's model containing time-dependent GEC values and alcohol abuse was built, GEC remained strictly related to survival, whereas alcohol abuse was no longer significant (Table 2).

DISCUSSION

Although this study does not meet the criteria for a controlled clinical trial, being a retrospective analysis of two cohorts of patients, it confirms that abstinence from alcohol in cirrhosis is associated to improvement in outcome, as observed in other series.[16,17]

The course of mean values of GEC during follow-up (Fig. 2) showed a progressive impairment in GEC in patients who continued alcohol abuse and eventually died, whereas in patients who started abstinence, an improvement in GEC was observed at the first follow-up visit, followed by a progressive impairment in GEC in patients who eventually died. From the course of GEC values in patients with the same number of follow-up visits (Fig. 3), a more precise evaluation of the course of GEC can be obtained. Indeed, in continuous drinkers a progressive impairment in GEC was observed, whereas patients who started abstinence experienced a significant improvement in GEC at the first follow-up visit, followed by a decrease in GEC, which probably represents the course of decrease in liver function because of the progression of liver disease, irrespective of the damage induced by alcohol.

A significantly shorter survival was observed in patients who continued drinking, and the results of Cox's regression analyses imply that the risk of death in patients with persistent alcohol abuse was approximately 3.5 times greater in comparison with patients who abstained throughout the study period, the risk increasing by 34% for any decrease of GEC by 1 mg/min/kg body weight.

Although persistent alcohol abuse and decrease in GEC were both significant predictors of death, they were not statistically independent, i.e., they were not expressions of different mechanisms leading to death. In fact, decrease in GEC incorporated most of the prognostic information coming from persistent alcohol abuse, and a 2-variable model showed that persistent alcohol abuse was no longer significant, when variations in GEC were taken into account. This implies that variations in risk of death occurring as a consequence of abstinence from alcohol may be predicted from changes in GEC, and that the mechanisms through which abstinence influences survival are strictly linked to the mechanisms which cause changes in GEC. This represents adherence to the second criterion proposed by Prentice.[4] Taken together with the strict association of decrease in GEC and survival,[7,8] this observation suggests that GEC may be a useful surrogate end point for survival in this clinical condition. This is particularly relevant, because established and verified surrogate end points are very rare.[18] Obviously, as frequently occurs in this kind of study, the probability of a type I error is not negligible, and a prospective validation of the present findings in future studies will be extremely useful to rule out this possibility.

In conclusion, abstinence from alcohol in patients with cirrhosis and alcohol abuse is associated with a longer survival. GEC keeps rather constant in survivors, and decreases progressively in those who eventually die, especially in those who continue alcohol abuse. Only abstainers show a transient improvement in GEC. Under these conditions the decrease in GEC can be considered an adequate surrogate end point

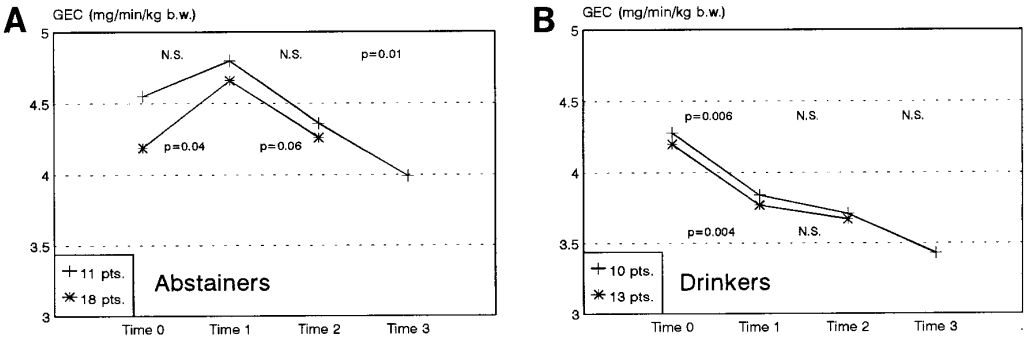

FIG. 3. Mean values of GEC in patients with three (*) or four (+) follow-up visits in patients who abstained (A) or who continued drinking (B). One-way analysis of variance showed significant difference in all series. Reported P values are for paired Student's t test among adjacent classes.

TABLE 2. Cox's Regression Models for 45 Patients With Cirrhosis

Model	Variable	β	β/SEM	P
Only alcohol abuse	Abuse	.62	2.09	.04
Only GEC (time-dependent)	GEC	−1.05	−3.97	.01
Alcohol abuse and GEC	GEC	−.97	−3.47	.01
(time-dependent)	Abuse	.32	.97	.33

for death in cirrhotic patients. When new therapies aimed at prolonging survival in cirrhosis by improving liver function or by slowing the progressive decrease of liver function will be available, the use of GEC as surrogate end point will be worth testing.

REFERENCES

1. Boissel JP, Collet JP, Moleur P, Haugh M. Surrogate endpoints: a basis for a rational approach. Eur J Clin Pharmacol 1992;43:235-244.
2. Fleming TR, Prentice RL, Pepe MS, Glidden D. Surrogate and auxiliary endpoints in clinical trials, with potential applications in cancer and AIDS research. Stat Med 1994;13:955-969.
3. Herson J. The use of surrogate endpoints in clinical trials (an introduction to a series of four papers). Stat Med 1989;8:403-404.
4. Prentice RL. Surrogate endpoints in clinical trials: definitions and operational criteria. Stat Med 1989;8:431-440.
5. Reichen J, Solioz M, Buehler H, Gonvers JJ, Knoblauch M, Lavanchy D, Malé PJ, et al. Low-dose interferon in chronic hepatitis non-A/non-B: effects on quantitative liver function and structure in a randomized controlled multicenter trial. Clin Investigator 1993;71:888-893.
6. Merkel C, Bolognesi M, Bellon S, Bianco S, Honisch B, Lampe H, Angeli P, et al. Aminopyrine breath test in the prognostic evaluation of patients with cirrhosis. Gut 1992;33:836-842.
7. Merkel C, Gatta A, Zoli M, Bolognesi M, Angeli P, Iervese T, Marchesini G, et al. Prognostic value of galactose elimination capacity, aminopyrine breath test, and ICG clearance in patients with cirrhosis. Comparison with the Pugh score. Dig Dis Sci 1991;36:1197-1203.
8. Reichen J, Widmer T, Cotting J. Accurate prediction of death by serial determinations of galactose elimination capacity in primary biliary cirrhosis: a comparison with the Mayo model. HEPATOLOGY 1991;14:504-510.
9. Marchesini G, Fabbri A, Bugianesi E, Bianchi GP, Marchi E, Zoli M, Pisi E. Analysis of the deterioration rates of liver function in cirrhosis, based on galactose elimination capacity. Liver 1990;10:65-71.
10. Tygstrup N. Determination of the hepatic elimination capacity (Lm) of galactose by single injection. Scand J Clin Lab Invest 1966;18(suppl):118-125.
11. Christensen E, Schlichting P, Fauerholdt L, Juhl E, Poulsen H, Tygstrup N. Changes in laboratory variables with time in cirrhosis: prognostic and therapeutic significance. HEPATOLOGY 1985;5:843-853.
12. Kaplan EL, Meier P. Nonparametric estimates from incomplete observations. J Am Stat Assoc 1958;53:457-481.
13. Lin DY, Fischl MA, Schoenfeld DA. Evaluation of the role of CD4-lymphocite count as surrogate endpoints in human immunodeficiency virus clinical trials. Stat Med 1993;12:835-842.
14. Cox DR. Regression models and life tables (with discussion). J Royal Stat Soc 1972;B34:187-220.
15. Christensen E, Schlichting P, Andersen PK, Fauereholdt L, Schou G, Pedersen BV, Juhl E, et al. Updating prognosis and therapeutic effect evaluation in cirrhosis with Cox's multiple regression model for time-dependent variables. Scand J Gastroenterol 1986;71:163-174.
16. Powell WJ Jr, Klatskin G. Duration of survival in patients with Laennec's cirrhosis. Am J Med 1968;44:406-416.
17. Brunt PW, Kew MC, Scheuer PJ, Sherlock S. Studies in alcoholic liver disease in Britain. I. Clinical and pathological patterns related to natural history. Gut 1974;15:52-65.
18. Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. Stat Med 1992;11:167-178.