Evaluation of Liver Function in Type 2 Diabetic Patients During Clinical Trials

Evidence that rosiglitazone does not cause hepatic dysfunction

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OBJECTIVE — Troglitazone treatment has been associated with idiosyncratic hepatic reaction leading to hepatic failure and death in some patients. This raises questions regarding whether all thiazolidinediones or peroxisomal proliferator–activated receptor-γ (PPAR-γ) agonists are hepatotoxic and whether data from clinical trials are adequate to detect a signal of potentially serious drug-related hepatotoxicity. The purpose of this study was to assess whether the idiosyncratic liver toxicity reported with troglitazone is molecule-specific or a thiazolidinedione class effect, based on liver enzyme data collected prospectively during phase 2/3 clinical trials with rosiglitazone, a new, potent, and specific member of the thiazolidinedione class.

RESEARCH DESIGN AND METHODS — This is an analysis of liver function in type 2 diabetic patients at baseline and serially in 13 double-blind, 2 open-label active-controlled, and 7 open-label extension studies of rosiglitazone treatment conducted in outpatient centers throughout North America and Europe. The study comprised >6,000 patients aged 30–80 years with type 2 diabetes. Patients underwent baseline liver function studies and were excluded from clinical trials if they had an alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase value 2.5 times greater than the upper limit of the reference range. The main outcome measures were liver enzyme levels, which were assessed at screening, at baseline, and every 4 weeks for the first 3 months of treatment and at 6- to 12-week intervals thereafter. Patients with at least one on-therapy ALT value >3 times the upper limit of the reference range were identified, and their case records examined in detail.

RESULTS — At baseline, 5.6% of the patients with type 2 diabetes (mean HbA_{1c} 8.5–9.0%) had serum ALT values between 1.0 and 2.5 times the upper limit of the reference range. On antidiabetic therapy, most of those patients (~83%) had a decrease in ALT values, many into the normal range. The percentages of all patients with an on-therapy ALT value >3 times the upper limit of the reference range during double-blind and open-label treatment were as follows: rosiglitazone-treated 0.32%, placebo-treated 0.17%, and sulfonylurea-, metformin-, or insulin-treated 0.40%. The respective rates of ALT values >3 times the upper limit of the reference range per 100 person-years of exposure were 0.29, 0.59, and 0.64.

CONCLUSIONS — No evidence of hepatotoxic effects was observed in studies that involved 5,006 patients taking rosiglitazone as monotherapy or combination therapy for 5,508 person-years. This is in keeping with hepatic data from clinical trials of another member of the class, pioglitazone, and in contrast to the clear evidence of hepatotoxic effects observed during the troglitazone clinical trial program. These findings suggest that the idiosyncratic liver toxicity observed with troglitazone is unlikely to be a thiazolidinedione or a PPAR-γ agonist class effect. Poorly controlled patients with type 2 diabetes may have moderate elevations of serum ALT that will decrease with improved glycemic control during treatment with rosiglitazone or other antihyperglycemic agents.

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In recent years, increasing recognition of the role of insulin resistance in the pathogenesis of type 2 diabetes (1–3) has heightened interest in therapeutic strategies that target insulin sensitivity rather than insulin secretion (4–7). The discovery of the selective peroxisomal proliferator–activated receptor-γ (PPAR-γ) agonist thiazolidinediones and the introduction of the first approved thiazolidinedione, troglitazone, were significant advances in the search for effective insulin-sensitizing agents (6,8–10). However, postmarketing reports of serious hepatic reactions to troglitazone, including fatal fulminant hepatitis (11–16), raised concerns about the safety of troglitazone and other members of this class. In the U.K., troglitazone was voluntarily withdrawn from the market, and in the U.S., the Food and Drug Administration (FDA) requested removal of the drug after prescribing information had been revised several times to include stronger warnings and guidelines for extensive monitoring of hepatic function in patients taking troglitazone (6,17,18).

Rosiglitazone is a new thiazolidinedione that has been shown to be highly effective in reducing insulin resistance and improving glycemic control in both animal models of diabetes and human type 2 diabetes (19,20). Although rosiglitazone and troglitazone are both members of the thiazolidinedione class, there are a number of biochemical and metabolic features

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FDA, Food and Drug Administration; PPAR-γ, peroxisomal proliferator–activated receptor-γ.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

that distinguish them with respect to their potential for hepatotoxicity.

As a PPAR-γ agonist, rosiglitazone is 100 times more potent than troglitazone (21); this difference in potency has translated into a clinical dose that is approximately one-hundredth that of troglitazone (4–8 vs. 400–600 mg). Although the two compounds share a common thiazolidinedione core, troglitazone is characterized by an α-tocopherol moiety, which may contribute to the formation of quinone metabolites (8,9,22), whereas rosiglitazone has an amino pyridyl side chain and no such metabolite (21). Troglitazone has been shown to be directly toxic to cultured rat hepatocytes at concentrations as low as 20 μmol/l (23,24), whereas rosiglitazone shows no toxicity at concentrations up to 100 μmol/l (limit of solubility) (23). Rosiglitazone and troglitazone also differ in their propensity to cause hepatotoxicity in preclinical species; troglitazone shows toxicity in all species tested (mouse, rat, and dog) (25). In contrast, rosiglitazone has produced elevation of alanine aminotransferase (ALT) only in dogs at concentrations four times greater than those found in humans at recommended doses. Finally, troglitazone undergoes significant enterohepatic circulation and is excreted primarily through the liver (26,27). Rosiglitazone is renally excreted and does not undergo enterohepatic recirculation (28). These preclinical data suggested that rosiglitazone may have little or no potential to cause hepatotoxicity during clinical use.

We describe in this communication the results of prospectively monitoring hepatic function in all patients who participated in randomized, controlled trials or in long-term extension studies of rosiglitazone through November 1999.

RESEARCH DESIGN AND METHODS

— This analysis includes data obtained from 13 double-blind clinical trials of rosiglitazone monotherapy or combination therapy and two ongoing, active-comparator clinical trials. The double-blind clinical trials were three short-term (8–12 weeks) dose-ranging studies using doses of 0.1–12 mg rosiglitazone per day, nine 26-week placebo-controlled clinical trials using 2-, 4-, or 8-mg total daily doses of rosiglitazone and one 52-week active-comparator trial of rosiglitazone and glyburide. The two ongoing, open-label active-comparator clinical trials are being conducted to assess the cardiac safety profile of rosiglitazone and are of greater than 24 months' duration.

All patients who completed the 13 double-blind clinical trials were eligible for entry into open-label extension studies with rosiglitazone 8 mg once daily or in divided doses. All of their data, including seven ongoing long-term extension studies, are included in this analysis. Patients who are in those open-label extension studies have received a total of up to 36 months of treatment with rosiglitazone alone or in combination with metformin, a sulfonylurea, or insulin.

In all studies, men and women between the ages of 30 and 80 years with a diagnosis of type 2 diabetes were eligible for inclusion. Women were required to be postmenopausal or currently using a reliable form of contraception. Patients with BMI values >38 or <22 kg/m^2 were excluded.

It should be noted that the rosiglitazone phase 2/3 clinical trial program was initiated before the detection of idiosyncratic hepatotoxicity in patients treated with troglitazone. Because patients with poor glycemic control may have diabetic hepatic steatosis or steatonecrosis, in all studies, patients were allowed to participate if they had total bilirubin, alkaline phosphatase, ALT, or aspartate aminotransferase (AST) levels ≤2.5 times the upper limit of the laboratory reference range. No other tests were performed to screen for preexisting liver disease (including hepatitis A, B, or C). Although hepatic function was monitored throughout the study period, study protocols did not contain criteria for stopping treatment on the basis of liver enzyme abnormalities.

Routine laboratory safety testing in patients who participated in rosiglitazone phase 2/3 studies included measurements of total bilirubin, alkaline phosphatase, ALT, and AST levels. Laboratory tests were performed at screening, at baseline, every 4 weeks for the first 3 months of treatment, and at 6- to 12-week intervals thereafter. Because ALT is a sensitive and specific marker of hepatocellular injury (29), on-therapy ALT levels >3 times the upper limit of the reference range were considered to be of "potential clinical concern." Patients with at least one on-therapy ALT value >3 times the upper limit of the reference range were identified, and their case records were examined in detail.

The proportion of patients in each treatment group with any on-therapy ALT value >3 times the upper limit of the reference range in controlled trials was determined. The rate of ALT values >3 times the upper limit of the reference range was calculated using as a denominator the number of person-years' exposure to rosiglitazone, placebo, or active comparator in all controlled and open-label extension trials through November 1999. Additionally, changes in ALT values were analyzed as a function of whether patients entered the trials with baseline values below or above (1.0–2.5 times) the upper limit of the reference range.

RESULTS

— During the 13 double-blind or 2 active comparator–controlled trials, 3,503 patients received rosiglitazone, 574 patients received placebo, and 828 patients received metformin or a sulfonylurea (Table 1). In the total clinical program (13 double-blind, 2 active-controlled, and their 7 open-label extensions), 5,006 patients received rosiglitazone, 574 patients received placebo, and 1,242 patients received metformin, a sulfonylurea, or insulin. Of the total number of patients receiving rosiglitazone, ~3,800 were on drug and monitored for ≥6 months, ~2,800 were on drug and monitored for ≥1 year, and ~1,000 were on drug and monitored for ≥2 years.

Baseline demographic and clinical characteristics were similar across all studies and all treatment groups. Approximately two-thirds of study participants were men. Most of the study participants were white, <65 years of age, and had BMI ≥27 kg/m^2. The two cardiac safety studies had higher proportions of men, patients <65 years of age, and patients with BMI <27 kg/m^2 than other studies in the phase 2/3 clinical trial program. Baseline glycemic control (mean HbA_{1c} and mean fasting plasma glucose) was similar across all groups.

Overall, mean values for serum ALT tended to decrease (−5.1 IU/l) in patients on rosiglitazone monotherapy. The prevalence of elevated serum ALT levels >3 times the upper limit of the reference range in the 13 double-blind–only studies was similar in the rosiglitazone (0.17%), placebo (0.17%), and sulfonylurea or metformin treatment groups (0.48%) (Table 1). In the 13 double-blind and 2 active-controlled trials and their 7 open-label extensions, the percentage of

Table 1—*Hepatic effects of thiazolidinediones in clinical trials (13 double-blind–only studies)*

	TRO trials		PIO trials		RSG trials		
	TRO	PBO*	PIO	PBO*	RSG	SU/MET	PBO
N	2,510	475	1,526	793	3,503	828	574
ALT >3× ULRR	48 (1.9)	3 (0.6)	4 (0.26)	2 (0.25)	6 (0.17)	4 (0.48)	1 (0.17)
ALT >10× ULRR	17 (0.68)	0					
Discontinued due to abnormal liver function	20 (0.8)	0					
Jaundice	2 (0.08)	0					

Data are *n* (%) unless otherwise indicated. *Includes antidiabetic background medications. Abbreviations. PBO, placebo; PIO, pioglitazone; RSG, rosiglitazone; SU/MET, sulfonylurea/metformin; TRO, troglitazone; ULRR, upper limit of reference range. Source for pioglitazone data: Takeda American Research and Development Center: *Actos (pioglitazone HCl) Complete Prescribing Information*. Lincolnshire, IL, Takeda Chemical Industries, 1999.

patients with on-therapy ALT levels >3 times the upper limit of the reference range was similar in the rosiglitazone (0.32%), placebo (0.17%), and sulfonylurea or metformin or insulin (0.40%) treatment groups.

A total of 16 patients who had taken rosiglitazone during the 13 double-blind and 2 active-controlled trials (7 patients) or 7 open-label extensions (9 patients) had elevated ALT >3 times the upper limit of the reference range. In controlled trials, six patients had transient ALT values >3 times the upper limit of the reference range occurring between weeks 4 and 18 of treatment; they all returned to within normal limits with continued rosiglitazone therapy. The remaining patient had normal ALT levels at screening but had a value >3 times the upper limit of the reference range at baseline (the day rosiglitazone and sulfonylurea treatment was started). That patient was treated for 7 weeks, during which time the ALT elevation persisted but did not increase. In the open-label extensions, nine patients taking rosiglitazone had elevations of ALT >3 times the upper limit of the reference range. In one patient, the enzyme elevation developed after halothane anesthesia, and it persisted at follow-up. One patient had an isolated elevation at 12 months of therapy, but his ALT levels were normal at follow-up, after the study ended. Four patients had a decrease in their ALT values to within the reference range or to <2.5 times the upper limit of the reference range. One patient still had an elevation at last observation, and two patients were withdrawn. One of these patients still had elevated enzymes 5 days after being withdrawn and the other patient was lost to follow-up.

Data on the rate of ALT values >3 times the upper limit of the reference range in the patients in the rosiglitazone clinical program were calculated as a function of the years of exposure to the various treatments (Table 2). There was no difference in the incidence of ALT elevations seen with rosiglitazone treatment compared with placebo or active comparators.

Additional analyses were performed to determine the effects of rosiglitazone on ALT levels in individuals who entered the studies with ALT values in the normal range as well as in those who entered the study with ALT elevations between the upper limit of the reference range and 2.5 times the upper limit of the reference range. Table 3 shows that ~3–4% of patients who entered the trials with normal liver function had an ALT elevation up to but <3 times the upper limit of the reference range, whether they received placebo or rosiglitazone. Furthermore, only 0.2% or fewer patients had elevations >3 times the upper limit of the reference range.

Among patients who entered the trials with ALT elevations between the upper limit and 2.5 times the upper limit of the reference range, there was only a 1.4% likelihood of increasing ALT levels to >3 times the upper limit of the reference range at any time on therapy and an 83% likelihood of having improved liver function by their last on-therapy measurement. This was similar to those treated with other active comparators (Table 4) and probably reflects an improvement of liver function secondary to improved metabolic control.

CONCLUSIONS — Rosiglitazone is a highly potent and selective PPAR-γ ligand; PPAR-γ agonist activity in adipocytes is ~100 times that of troglitazone and 30 times that of pioglitazone (20,30,31). Clinical studies attest to its effectiveness in improving insulin resistance and glycemic control in patients with type 2 diabetes. The major question about the use of new PPAR-γ agonists in general and thiazolidinediones in particular is whether the liver toxicity observed with troglitazone is unique to troglitazone or represents a class effect.

The ability to detect the potential of a new drug to cause serious hepatic disease has been difficult. Recently, the U.S. FDA assessed, in detail, the current state of knowledge and existing methodology for

Table 2—*Rate of ALT values >3 times the upper limit of the reference range per 100 patient-years of exposure in 13 double-blind, 2 active-controlled, and 7 open-label extension studies***

	All rosiglitazone (*N* = 5,006)	Placebo (*N* = 574)	Metformin, sulfonylurea, or insulin (*N* = 1,242)
Person-years	5,508	170	778
Incident cases	16	1	5
Rate/100 person-years	0.29	0.59	0.64

*Patients with baseline ALT >3 times the upper limit of the reference range were excluded from this analysis. There were three such patients: one who received a sulfonylurea + rosiglitazone; one who received a sulfonylurea alone; and one who received metformin alone in a double-blind, controlled trial and metformin + rosiglitazone in an open-label extension study.

Table 3—*Incidence of liver abnormalities occurring in patients with normal baseline liver function (less than the upper limit of the normal reference range)*

	RSG monotherapy			Placebo		
	N	>ULRR (%)	>3× ULRR	*N*	>ULRR (%)	>3× ULRR (%)
ALT	2,844	4.3	0.1	530	3.4	0.2
Alkaline phosphatase	2,856	2.2	0.1	514	8.2	0.0
AST	2,846	4.1	0.0	512	2.5	0.2
Total bilirubin*	2,944	1.8	0.2	536	2.2	0.0
	RSG + metformin			Metformin		
	N	>ULRR (%)	>3× ULRR	*N*	>ULRR (%)	>3× ULRR (%)
ALT	513	3.7	0.0	204	3.9	0.0
Alkaline phosphatase	525	0.6	0.0	217	3.7	0.0
AST	529	3.2	0.2	215	1.4	0.0
Total bilirubin*	529	1.1	0.4	215	4.7	0.5
	RSG + sulfonylurea			Sulfonylurea		
	N	>ULRR (%)	>3× ULRR	*N*	>ULRR (%)	>3× ULRR (%)
ALT	901	6.1	0.2	789	7.9	0.1
Alkaline phosphatase	899	1.4	0.0	791	3.3	0.0
AST	925	5.0	0.0	807	4.0	0.1
Total bilirubin*	916	2.3	0.0	788	4.1	0.3
	RSG + insulin			Insulin		
	N	>ULRR (%)	>3× ULRR	*N*	>ULRR (%)	>3× ULRR (%)
ALT	508	2.8	0.2	188	3.7	0.0
Alkaline phosphatase	508	1.4	0.0	184	4.3	0.0
AST	526	3.2	0.2	189	0.5	0.0
Total bilirubin*	527	1.1	0.0	194	1.0	0.0

*Total bilirubin is 1.5× ULRR. RSG, rosiglitazone; ULRR, upper limit of normal.

examining hepatotoxic events associated with pharmaceuticals (32). Serious liver injury leading to hepatic failure and death is uncommon and frequently referred to as "idiosyncratic," meaning that it is unpredictable and, because of its rarity, is often undetected in placebo or comparator-controlled clinical trials. However, Hyman Zimmerman noted that clinical trials can detect signals of the potential of a drug to cause serious liver disease when it is used in large populations (32).

In standard practice, an elevation of serum transaminase >3 times the upper limit of the reference range that statistically exceeds that of the placebo group is a potential signal for causing serious liver disease. The higher the transaminase level, the more ominous the signal and the less important the comparison with the placebo group. Particularly ominous are transaminase elevations that occur in combination with elevations in serum bilirubin or jaundice. In his book on hepatotoxicity, Hyman Zimmerman noted that transaminase elevations and jaundice are particularly ominous, with ~10% of such patients dying of drug-induced liver injury (32).

During clinical trials with troglitazone, 0.68% of patients had ALT elevations >10 times the upper limit of the reference range and 0.08% developed jaundice (Table 1). Based on these data, one could predict that liver failure might occur in 80 per 100,000 individuals in a troglitazone-treated population. In clinical trials of rosiglitazone, the lack of ALT elevations >10 times the upper limit of the reference range or significant elevations in serum bilirubin indicates no signal of potential hepatic toxicity and may predict a lack of clinical liver failure when administered to large populations.

The lack of evidence of hepatotoxicity in the clinical trials with rosiglitazone is not unexpected, as preclinical observations indicate that rosiglitazone and troglitazone are markedly different in their metabolism and hepatic effects. Troglitazone is metabolized by the liver and converted into an inactive sulfate conjugate, an oxidative quinone metabolite, and a glucuronide metabolite (22,26,27). This differs from the metabolism of rosiglitazone, which proceeds via *N*-demethylation and aromatic hydroxylation (SmithKline Beecham, data on file). Troglitazone is concentrated in the liver of rats 15- to 20-fold more than in plasma (25), whereas rosiglitazone is not significantly concentrated in the liver (one- to twofold higher than plasma levels) (SmithKline Beecham, data on file). Troglitazone and its metabolites recirculate through the biliary system, and only 3.1% are excreted in the urine

(8). In contrast, rosiglitazone and its metabolites do not recirculate through the biliary system, and the kidney excretes 65%. Furthermore, in vitro comparison of the toxicity of troglitazone and rosiglitazone in cultured rat hepatocytes demonstrated that troglitazone was directly cytotoxic at concentrations as low as 20 μmol/l, whereas rosiglitazone, at its limit of solubility (100 μmol/l), was not (23).

Other evidence is available that demonstrates clinically meaningful differences between troglitazone and rosiglitazone in terms of hepatic metabolism. At clinically relevant doses, troglitazone is a potent inducer of the CYP3A4 enzyme system (17,33–37). As a result, troglitazone may interact significantly with many other drugs, because CYP3A4 is believed to be partially or completely responsible for the metabolism of ~50% of xenobiotics metabolized by the cytochrome P450 system (38), including calcium channel blockers, benzodiazepines, HMG-CoA reductase inhibitors, human immunodeficiency virus protease inhibitors, and immunosuppressive agents (39). However, rosiglitazone is metabolized primarily by CYP2C8 and has shown no clinically significant interactions with CYP3A4-metabolized substrates such as nifedipine and oral contraceptives (40).

Abnormal liver function tests, particularly ALT elevations, are not unexpected during long-term follow-up of patients with type 2 diabetes. Our large prospective database of longitudinal changes in liver function tests in patients with type 2 diabetes provides useful information on liver function in patients in whom glycemic control is improved (active treatments) versus those in whom it is stable or deteriorates modestly (placebo-treated controls). At baseline entry into the studies, when the mean HbA_{1c} levels were between 8.5 and 9.0%, 381 of 6,822 patients (5.6%) had serum ALT values between 1.0 and 2.5 times the upper limit of the reference range. After placebo treatment, 38.7% of those with such elevations had a decrease of serum ALT into the normal range and an equal number had an increase but did not exceed three times the upper limit of the reference range. In contrast, 66% of patients with type 2 diabetes given an active antihyperglycemic agent decreased their serum ALT levels into the normal range, whereas 12.9% had an increase but were still <3 times the upper limit of the reference range and 2.0% increased to >3 times the upper limit of the reference range.

In the large population of patients with type 2 diabetes who entered the studies with serum ALT levels within the normal range, we found that ~4.0% had a serum ALT elevation at some time during the trial that was >1.0 and <3.0 times the upper limit of the reference range, and 0.1–0.2% exceeded three times the upper limit of the reference range. These findings probably reflect changing degrees of hepatic steatosis in a diabetic population.

Many reports document an increase in liver disease occurring in type 2 diabetic patients. Salmela et al. (41) noted that 22.9% of 118 outpatients with type 2 diabetes had an elevated ALT value during random evaluation. These abnormalities were rarely more than two times the upper limit of the reference range, and obesity and poor glycemic control increased the frequency and severity of the abnormalities. Jick et al. (42), in a recent epidemiologic study of 44,406 patients with type 2 diabetes, found that during follow-up, 605 patients developed liver disease (incidence rate 0.53 per 100 person-years), ranging from hepatitis to gallbladder disease to hepatosteatosis to carcinoma involving the liver or biliary ducts.

Therefore, in evaluating any drug for its potential to cause hepatotoxicity, an appropriate control population must be included. This is true in both controlled trials and postmarketing surveillance. Isolated postmarketing cases can show an association of treatment with occurrence of hepatotoxicity, such as has been reported with rosiglitazone in two case reports, but are unlikely to provide information about causality because of confounding factors and lack of an adequate control population (43,44).

The FDA-approved prescribing information for rosiglitazone states that ALT elevations in patients treated with rosiglitazone in the preapproval clinical trials were reversible and were not clearly causally related to therapy with rosiglitazone. It further states that very rarely postmarketing reports of hepatic disease during rosiglitazone treatment have been received, although causality has not been established. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, the FDA recommends measurement of liver enzyme levels before initiation of rosiglitazone and pioglitazone therapy and at 2-month intervals for the first 12 months of therapy and periodically thereafter.

The additional clinical data presented and analyzed here and the preclinical studies noted provide some additional support to suggest that rosiglitazone

Table 4—*Last on-therapy value for patients with baseline ALT values ≥1.0 and <2.5 times the upper limit of the normal reference range*

	Rosiglitazone (*N* = 5,006)	Metformin (*N* = 219)	Sulfonylurea (*N* = 829)	Insulin (*N* = 194)	Placebo (*N* = 574)
Baseline value >ULRR*	295 (5.9)	16 (7.3)	33 (4.0)	6 (3.1)	31 (5.4)
Change in baseline values with treatment†					
No change	11 (3.7)	1 (6.3)	1 (3.0)	0 (0.0)	1 (3.2)
BL value decreased to ≤ULRR	205 (69.5)	11 (68.8)	12 (36.4)	3 (50.0)	12 (38.7)
BL value decreased but still >ULRR	40 (13.6)	2 (12.5)	10 (30.3)	2 (33.3)	6 (19.4)
BL value increased above baseline but still <3× ULRR	35 (11.9)‡	0 (0.0)	9 (27.3)	1 (16.7)	12 (38.7)
BL value increased to >3× ULRR	4 (1.4)	2 (12.5)	1 (3.0)	0 (0.0)	0 (0.0)

Data are *n* (%). *Percent of total patients, †percent of initially abnormal patients, ‡only four patients (1.6%) had an ALT >3 × ULRR. BL, baseline, ULRR, upper limit of normal range.

treatment is unlikely to be causally related to an increased risk of hepatotoxicity.

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