Diabetes Metab (Paris)
2001, 27, 305-313

REVIEW

THIAZOLIDINEDIONES AND LIVER TOXICITY

A. J. SCHEEN

SUMMARY - Thiazolidinediones or glitazones specifically target insulin resistance. They have proven efficacy for reducing plasma glucose levels of type 2 diabetic patients treated with diet alone, sulphonylureas, metformin or insulin. In addition, they may be associated to some improvement of cardiovascular risk profile. However, troglitazone, the first compound approved by the FDA in the US, proved to be hepatotoxic and was withdrawn from the market after the report of several dozens of deaths or cases of severe hepatic failure requiring liver transplantation. It remains unclear whether or not hepatotoxicity is a class effect or is related to the unique tocopherol side chain of troglitazone. Rosiglitazone and pioglitazone, two other glitazones, appear to have similar efficacy on blood glucose control of type 2 diabetic patients as compared to troglitazone. In controlled clinical trials, the incidence of significant increases in liver enzyme levels (ALT) was similar with rosiglitazone or pioglitazone as compared to placebo, whereas troglitazone was associated with a threefold greater incidence. In contrast to the numerous case reports of acute liver failure in patients receiving troglitzone, only two cases of severe reversible liver failure have been reported in patients treated with rosiglitazone, with a causal relationship remaining uncertain. Furthermore, no single case of severe hepatotoxicity has been reported yet with pioglitazone. While regular monitoring of liver enzymes is still recommended and more long-term data are desirable, current clinical evidence supports the conclusion that rosiglitazone and pioglitazone do not share the hepatotoxic profile of troglitazone.

Key-words: hepatitis, liver toxicity, pioglitazone, rosiglitazone, thiazolidinediones, troglitazone.

RÉSUMÉ - **Thiazolidinediones et toxicité hépatique.**
Les thiazolidinediones, encore appelées glitazones, ont pour cible l'insulinorésistance. Elles ont prouvé leur efficacité pour diminuer la glycémie de patients diabétiques de type 2 traités par régime seul, sulfonylurées, metformine ou insuline. De plus, elles peuvent améliorer le profil de risque cardio-vasculaire. Cependant, la troglitazone, la première glitazone acceptée par la FDA aux Etats-Unis, s'est révélée être hépatotoxique et a dû être retirée du marché après la survenue d'une série de décès ou de cas d'insuffisance hépatocellulaire terminale requérant une transplantation. La question de savoir si l'hépatotoxicité est un effet de classe propre aux glitazones ou si elle est spécifiquement liée à la chaîne latérale de la troglitazone reste ouverte. La rosiglitazone et la pioglitazone, deux autres glitazones ont démontré une efficacité sur le contrôle glycémique des patients diabétiques de type 2 apparemment comparable à celle de la troglitazone. Dans des essais cliniques contrôlés, l'incidence d'une élévation significative des transaminases hépatiques a été similaire avec la rosiglitazone ou la pioglitazone par comparaison à celle observée sous placebo, alors que la troglitazone était associée à une incidence triple. Au lieu des nombreux cas d'insuffisance hépatique aiguë rapportés sous troglitzone, seulement deux cas d'hépatotoxicité sévère réversible ont été décrits avec la rosiglitazone, sans qu'une relation causale ait pu être définitivement prouvée. Aucun accident de ce type n'a encore été rapporté avec la pioglitazone. Bien qu'une surveillance régulière des enzymes hépatiques reste recommandée et que des données complémentaires de pharmacovigilance soient certainement souhaitables, l'évidence clinique actuelle plaide pour la conclusion que ni la rosiglitazone ni la pioglitazone ne partage le risque d'hépatotoxicité de la troglitazone.

Mots-clés : hépatite, toxicité hépatique, pioglitazone, rosiglitazone, thiazolidinediones, troglitazone.

✍ *: A.J. Scheen, Division of Diabetes, Nutrition & Metabolic Disorders, Department of Medicine, CHU Sart Tilman, B-4000 Liège, Belgium.*
E-mail: Andre.Scheen@chu.ulg.ac.be
Received : February 8, 2001

Division of Diabetes, Nutrition and Metabolic Disorders, and Division of Clinical Pharmacology and Therapeutics, Department of Medicine, CHU Sart Tilman, Liège, Belgium.

Decreased insulin sensitivity is a key defect of patients with type 2 diabetes and represents a major target for the treatment of such patients, especially when obesity is present [1-3]. Insulin resistance may not only worsen hyperglycaemia but also may trigger various metabolic disturbances (arterial hypertension, dyslipidaemias, etc.) that all contribute to accelerate atherosclerosis and worsen cardiovascular prognosis [4].

Thiazolidinediones (TZDs) are a new class of oral antidiabetic agents that directly target insulin resistance [5-10]. Drugs of this class act as ligands for the gamma subtype of the peroxisome proliferator-activated receptor (PPAR-γ), which is directly involved in the regulation of genes controlling glucose homeostasis and lipid metabolism [11, 12]. Troglitazone, the first TZD to be approved for clinical use, has proven effective in reducing glycaemia in patients with type 2 diabetes [13-17]. Such new insulin sensitizers may not only improve blood glucose control, but also improve cardiovascular risk profile and possibly outcome [18, 19].

Clinical development of the TZDs was initially delayed because of unacceptable poor efficacy or toxicity which led to the discontinuation of ciglitazone and englitazone after the phase II clinical trials [8]. Three compounds, troglitazone [13, 16], rosiglitazone [20], and pioglitazone [21], appeared to have acceptable toxicity profiles in clinical trials and were subsequently approved by the Food and Drug Administration in the U.S. The thiazolidine-2-4-dione structure is common to all drugs of this class, the difference lying in their side chains which may modify the pharmacological activity and side effects. Soon after its launch in 1997, the first available glitazone, troglitazone, proved to be associated with hepatotoxicity and the report of several dozens of cases of severe liver failure and death [22, 23] led to its withdrawal from the US market in March 2000.

The problem of drug-induced hepatic disorders is a major concern in pharmacovigilance studies [24, 25]. As liver abnormalities are common in obese subjects, especially in patients with type 2 diabetes [26-28], it is important to use strict criteria of drug-induced liver disorders [29] and to be cautious before considering a causal relationship between abnormal liver tests and previous drug administration [30]. The present review aims at comparing the liver effects of the three main TZDs, troglitazone, rosiglitazone and pioglitazone, in order to answer the important question: is hepatotoxicity a class effect concerning all TZDs or is it specifically related to troglitazone [31-33]?

■ LIVER TOXICITY AND TROGLITAZONE

A few months after its approval in the US for the treatment of type 2 diabetes in January 1997 [13-17] and soon after the report of first cases of severe hepatotoxicity [22], troglitazone was withdrawn from the market in the UK (late 1997, i.e. only a few weeks after its launch) [34]. This was followed by the abandonment of the overall approval process and all clinical trials in Europe [35, 36]. In the US and in Japan, the manufacturer first introduced a series of labelling changes for troglitazone recommending close monitoring of liver enzyme levels and search for clinical signs of liver dysfunction [37]. Finally, and almost two years after call to ban troglitazone [38, 39], hepatotoxicity led to the withdrawal of the drug in March 2000 [40].

Observations in clinical trials

In early clinical trials with troglitazone, elevations of serum aminotransferase levels were noted *(Fig. 1)*. During the combined US trials of troglitazone, 2 510 patients received troglitazone (1 134, i.e. 45% took the drug for at least 6 months) and 475 received placebo. Serum ALT was elevated to $\geq 3 \times$ upper limit of normal range (ULN) in 1.9% (48/2 510) of patients receiving troglitazone compared with 0.6% (3/475) of those receiving placebo [22, 32]. Increased ALT led to discontinuation of treatment in 0.8% (20/2 510) of troglitazone-treated patients and in no placebo-treated patients. Of these 20 patients, 12 had peak serum ALT concentrations $\geq 10 \times$ ULN while five had concentrations $\geq 20 \times$ ULN. Overall, 18 of these patients were judged by investigators to have significant hepatocellular injury. Liver biopsy performed on two of these patients was consistent with a hepatocellular drug reaction and two other patients had additional cholestatic features. Most of the patients with ALT $\geq 3 \times$ ULN did not experience symptoms of liver dysfunction and thus were only detected by monitoring during the clinical trials. Two of 2 510 patients (0.08%), i.e. two of the 12 with ALT $> 10 \times$ ULN, experienced jaundnice [32]. The onset of the serum ALT elevations was typically delayed, with only one patient having an elevation during the first month of therapy. In most patients, the peak values occurred between the third and seventh months (mean 147 days; range, 1 to 287). In the 20 patients in whom therapy was discontinued, serum ALT concentrations returned to baseline (mean, 55 days; range, 8 to 142) [22]. In other 20 patients in whom therapy was continued despite serum ALT levels $\geq 3 \times$ ULN (5 of whom had ALT $\geq 10 \times$ ULN), ALT values also returned to baseline, indicating that in some patients the liver is able to adapt to injury associated with troglitazone [22].

Case reports of severe hepatotoxicity

Numerous cases of acute liver failure due to troglitazone appeared in the literature as “case reports” or

"letters to the Editor" [22, 23, 41-56]. By June 1998, the FDA had received 560 reports of troglitazone-related hepatotoxicity, including 24 cases of acute liver failure. At the time of the FDA Advisory Committee Meeting in March 1999, 43 cases of acute liver failure were reported. Nine of these patients received liver transplantation and a total of 28 had died [32]. On average, they had been on medication for 116 days (4-236 days); 69% were taking 400 mg/day, 20% were taking 200 mg/day and 11% were taking 600 mg/day. This reflects the usual therapeutic dosage distribution and does not suggest a dose-related effect. At the time of diagnosis, 89% of the patients had jaundice and in 62% of cases it was the first symptom. Histological material was available for several of the patients and showed a consistent pattern of hepatocellular necrosis with bridging necrosis and fibrosis or collapse [32].

In a systematic analysis of adverse events reported to the US FDA, Kohlroser *et al.* [23] reviewed 46 MedWatch reports considered suspicious for hepatitis. Striking results include the greater than 2: 1 female: male ratio (suggesting that women may be more susceptible, even it may also be that more women than men have taken troglitazone), the marked variability in cumulative drug dose (1 200-78 000 mg), and duration of therapy (6-195 days). Most patients had predominantly hepatocellular or mixed heptocellular-cholestatic-type injury.

In a series of 35 cases of liver dysfunction in Japan, elevation of ALT typically occurred within 2 to 5 months of starting troglitazone therapy [57]. Upon discontinuation of the drug, ALT levels generally declined rapidly, usually to less than half of the ALT peak level within 4 weeks. Interestingly, total bilirubin levels at the time of discontinuation of troglitazone might be a possible prognostic indicator. An investigation by the Ministery of Health and Welfare in Japan on the side effects of troglitazone showed there had been 110 cases of liver dysfunction, 7 of which resulted in death until March 1998 [58]. A characteristic typical of the patients who died was a rise in the bilirubin level. In a recent paper, it was stated that in Japan 153 diabetic patients treated with troglitazone developed severe hepatitis and 8 of them died of drug-side effects [59] *(Fig. 2)*.

There is disagreement as to the exact number of "validated" deaths associated with troglitazone in the US. The incidence of liver-related death or transplant appears to average approximately one case in 50 000-60 000 patients [16, 39]. Focusing specifically on liver-related deaths, the risk associated with troglitazone appears to have steadily declined from 1 in about 40 000 prior to the inclusion of liver enzyme monitor-

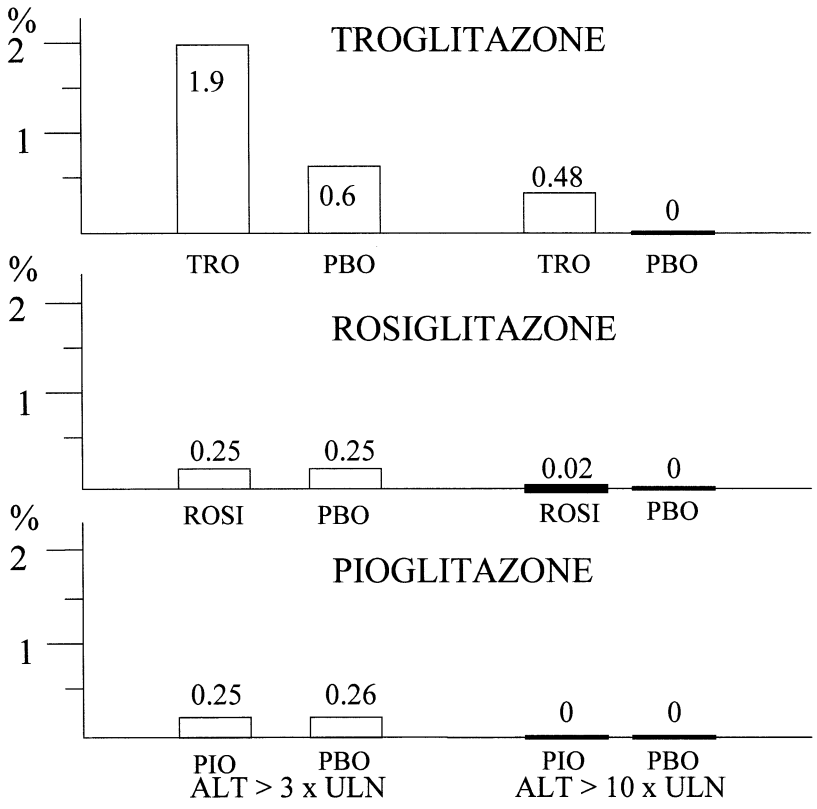

FIG. 1. *Comparison of the incidence (%) of elevated alanine aminotransferase (ALT) levels in controlled clinical trials with troglitazone (TRO, n = 2 510), rosiglitazone (ROSI, n = 3 314) and pioglitazone (PIO, n = 1 526) as compared to placebo (PBO). ULN: upper limit of normal range.*

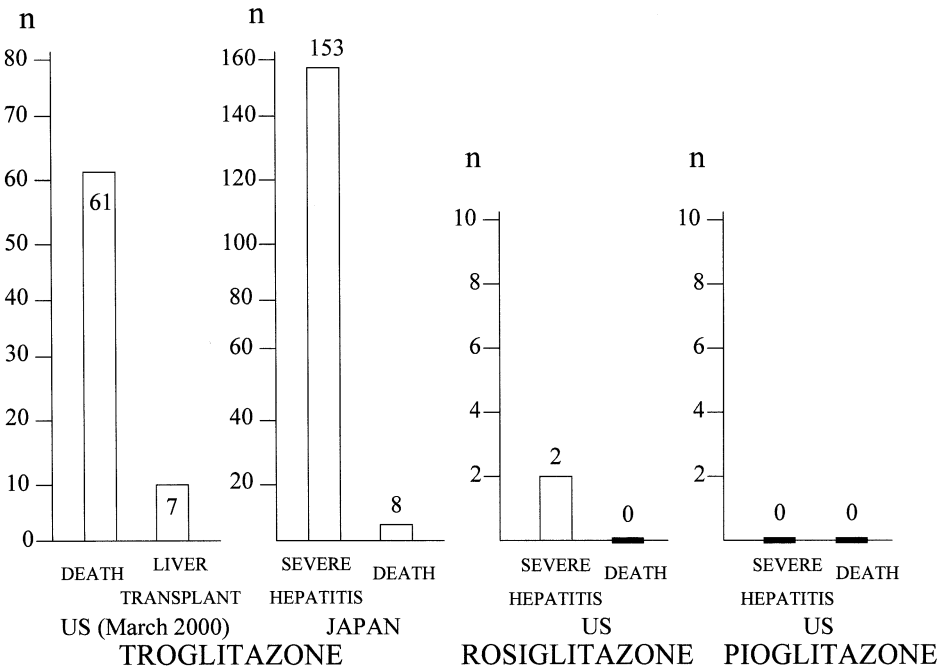

FIG. 2. *Comparison of reported cases (n) of severe hepatitis, liver transplant and death related to troglitazone, rosiglitazone or pioglitazone therapy in type 2 diabetic patients.*

ing in the product labelling (before October 1997) to approximately 1 in 100 000 among patients beginning therapy in 1998, i.e. after the incorporation of a boxed warning and increased monitoring requirements in the product labelling [16]. Thus, even if learning to use troglitazone was helpful [60], reason for concern still remained [61], and finally the drug was withdrawn from the US market in March 2000 [40]. By this time, the FDA had received 61 reports of fatal hepatotoxicity associated with the drug and 7 cases requiring liver transplantation *(Fig. 2)*.

Cause of troglitazone hepatotoxicity

There have been a few reports of fulminant hepatic failure in which pathological examinations of the entire liver were made [42, 43, 50]. Extensive histological studies may be informative about the mechanism of the liver failure attributable to troglitazone. The mechanism of drug-induced liver injury can be classified into intrinsic (direct toxic) and idiosyncratic [25, 62]. In less severe cases of troglitazone-induced hepatitis, liver biopsies were performed in two patients (including one with jaundice) and demonstrated the hepatocellular nature of the injury, which was consistent with an idiosyncratic drug reaction [22]. However, the mechanism of troglitazone-induced fulminant hepatitis remains obscure. A first autopsy case of a Japanese diabetic patient treated with troglitazone who died from fulminant hepatitis indicated that hypersensitivity may have played an important role in the development of liver damage [43]. This assumption was based upon the positive results of a drug-induced lymphocyte stimulation *in vitro* test and the presence of eosinophilic infiltration. In another autopsy case of fatal subacute hepatic failure after administration of troglitazone, Japanese authors came to the conclusion that the causative mechanism of liver dysfunction may be "metabolite aberration, as a result of accumulation of hepatotoxic metabolite(s), in a category of idiosyncratic liver injury" [50].

The patients with elevated ALT values after troglitazone did not have fever, rash, or eosinophilia, making a classic immune mechanism unlikely [22]. The hepatotoxicity observed with troglitazone may be related to its alpha tocopherol side chain which has been shown to scavenge free radicals in vitro and may have protective properties against oxidant stress [63]. It is known, indeed, that the basic quinone structure of alpha tocopherol is common to other drugs (such acetaminophen) which are subject to CYP2E1-mediated oxidation reactions forming free radicals which are hepatotoxic [29]. It is not known whether patients at risk for troglitazone hepatotoxicity have a polymorphism in cytochrome P-450 or other metabolizing enzyme expression that produces more of a toxic, highly reactive intermediate.

The use of hepatocyte cultures may be helpful for the study of hepatotoxicity compounds [64]. Studies in human and porcine hepatocyte cultures suggested

that the inhibition of troglitazone sulfation may result in increased hepatotoxicity due to exposure to parent drug, or increased metabolism by alternate pathways [65]. Interestingly, studies in rat hepatocyte culture showed that troglitazone, but not rosiglitazone, is hepatotoxic, an observation which is in accordance with clinical experience in humans [66].

Recent information suggested that PPAR-gamma receptors may be important in control the activation state of hepatic stellate cells (HSCs) [67]. HSCs represent the key cellular elements in the liver wound healing and development of hepatic fibrosis. Upon liver injury, HSCs acquire the ability to proliferate and migrate toward the damage areas and increase the production of extracellular matrix components. In addition, activated HSCs regulated the recruitment of inflammatory cells via secretion of chemotactic factors, including chemokines, and immunomodulatory cytokines such as interleukin (IL)-10. Activation of PPAR-gamma such as obtained with troglitazone has been shown to modulate profibrinogenic and proinflammatory actions in HSCs [68]. Thus, although troglitazone-associated hepatotoxicity is likely to represent an idiosyncratic reaction in most cases, the medical community will need to be alert to the possibility that interference with these receptors may cause hepatic dysfunction [67]. If this is true, caution should be recommended with all glitazones.

■ LIVER TOXICITY AND ROSIGLITAZONE

The pharmacological and clinical characteristics of rosiglitazone were extensively reviewed recently [20, 69-71]. Controlled clinical trials have proven its efficacy to improve the blood glucose control of patients with type 2 diabetes treating with diet alone [72-74], sulphonylurea [75], metformin [76] or insulin [20]. Rosiglitazone was approved by the FDA and launched in the US in May 1999. The European Agency for the Evaluation of Medicinal Products gave its approval in spring 2000, although with severe restrictions of clinical use: monotherapy and combination with insulin were excluded and only the combination with either sulphonylurea or metformin was approved [69].

Observations in clinical trials

In a total of 4 598 diabetic patients who have received rosiglitazone in clinical trials (3 314 of them for six months or more, for a total of 3 673 patient-years of exposure), the incidence of liver abnormalities (defined as any ALT elevation $\geq 3 \times$ ULN) was low (0.25%), and similar to that observed in placebo-treated patients (0.25%) [77] *(Fig. 1)*. Only one patient on rosiglitazone (0.02%) had a $\geq 10 \times$ ULN elevation in ALT compared to 12 patients (0.48%) on troglitazone [32].

In November 1999, exposure to rosiglitazone in clinical trials has substantially increased and comprised over 5 000 patient years including more than 1 000 patients treated for $\geq$ 2 years [78]. For all rosiglitazone-treated patients (including monotherapy and combination with sulphonylurea or metformin), the rate of ALT $\geq 3 \times$ ULN is 0.30 cases per 100 patient years, compared to 0.59 cases per 100 patient years for placebo-treated patients and 0.73 cases per 100 patient years for sulphonylurea- or metformin-treated patients. Thus, the current clinical trial experience with rosiglitazone indicates no evidence of troglitazone-like hepatotoxicity. On the contrary, recent data showed a trend to lower incidence of elevated ALT levels in type 2 diabetic patients receiving rosiglitazone than in those treated with placebo or other oral antidiabetic agents. This favourable tendency should be confirmed in further studies, but may be explained by the rosiglitazone-induced reduction of insulin resistance, a metabolic state which has been shown to be associated with fatty liver and NASH [27]. Indeed, a recent study showed that troglitazone prevents fatty changes of the liver in obese diabetic rats, presumably by reducing insulin resistance and improving the metabolic profile [79].

■ CASE REPORTS OF HEPATOTOXICITY

Two reports of acute hepatotoxicity attributed to rosiglitazone appeared in the literature [80, 81] *(Fig. 2)*. As these two reports are unique, they deserve further consideration. In a 69-year-old man, after 21 days of rosiglitazone therapy at a daily dose of 4 mg, severe hepatic failure developed and the patient became comatose [81]. As reported by the Authors, the patient developed nonspecific symptoms during rosiglitazone treatment that in retrospect probably reflected acute liver injury within one week of the start of rosiglitazone therapy. The patient was managed with intensive medical care and he gradually improved over the subsequent two weeks after rosiglitazone cessation. Other causes of hepatic failure, such as viruses and toxins, were excluded. This patient was also taking verapamil and pravastatin, both of which can cause hepatitis, but he had been received these drugs for more than one year without any problem. A liver biopsy was not performed. It was possible that ischemic hepatitis ("shock liver") played a superimposed role in this patient's hepatic dysfunction. However, according to the Authors, ischemia alone was unlikely to explain the patient's initial clinical picture and the decrease in the serum albumin level which was associated with the patient's illness is not typically associated with shock liver [81]. However, this interpretation was challenged by three independent hepatologists whose opinion was asked by Smith Kline Beecham Pharmaceuticals [82]. They concluded that this patient's liver injury was probably the result

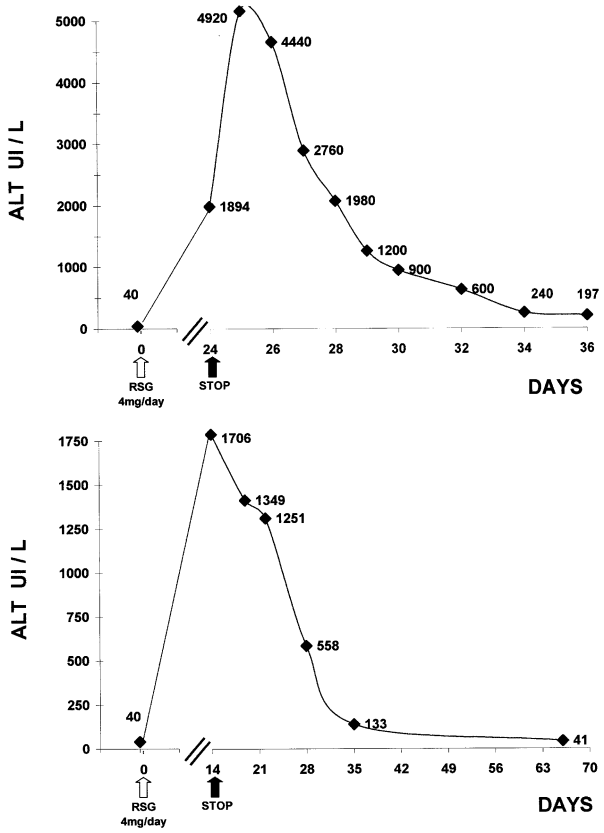

FIG. 3. *Changes in alanine aminotransferase (ALT) levels in two patients in whom severe but rapidly reversible hepatotoxicity was attributed to rosiglitazone (RSG) therapy: case of reference 81 (upper panel) and case of reference 80 (lower panel).*

of ischemia and not rosiglitazone. Indeed, the pattern and time course of biochemical abnormalities were characteristic of ischemic hepatitis, particularly the decrease in serum aspartate aminotransferase from greater than 11 000 U/L to normal within 9 days *(Fig. 3*, upper panel*)*. Such high and rapidly normalizing serum aminotransferase levels are unusual for most cases of drug-induced liver disease and have not been characteristic of troglitazone-induced liver dysfunction [22].

A 61-year-old man receiving rosiglitazone, 4 mg/day, for 2 weeks presented with anorexia, vomiting, and abdominal pain [80]. The patient noted the onset of his symptoms 8 days after starting rosiglitazone therapy. On admission, liver function tests revealed severe hepatocellular injury. ALT levels peaked at day one (1 706 U/L; normal range 0-40) *(Fig. 3*, lower panel*)*. Total bilirubin levels remained within the normal range while direct bilirubin levels were mildly and transiently elevated. Serum albumin levels were markedly decreased (minimal value: 2.3 g/L). However, at no time were signs or symptoms of hepatic failure observed. Discontinuation of rosiglitazone led to rapid improvement of liver function and resolution of symptoms. Serological tests excluded viral hepatitis. The patient's medical history included chronic obstructive pulmonary disease, a remote history of alcoholism and intermittent headache. He reported no recent alcohol intake, but he regularly used acetaminophen at a dose of three to four tablets daily before admission. However, his acetaminophen level on admission was within the therapeutic range, which made the diagnosis of acetaminophen toxicity unlikely. The Authors concluded that liver injury was caused by rosiglitazone in this patient and probably involved an idiosyncratic process. They proposed that patients receiving rosiglitazone should have liver enzyme levels monitored earlier and more frequently than initially recommended. However, as pointed out later on [83], this case was not only clouded by a history of alcohol abuse and acetaminophen use, but also by concomitant administration of zafirlukast, a compound which may provoke hepatitis and hyperbilirubinemia and, in rare cases, hepatic failure and inhibits one of the metabolic pathways for the clearance of rosiglitazone, the cytochrome P450 2C9 pathway.

These two reports [80, 81], even if alternative causes for hepatic failure have been suggested [82, 83] underline the need for further investigations into the potential hepatotoxicity of rosiglitazone and other drugs of the glitazone family. However, after more than 18 months of commercialization of rosiglitazone in the US, the number of case reports of rosiglitazone-related hepatotoxicity remains extremely low, and indeed much lower than the corresponding one of troglitazone-induced cases of liver dysfunction after the same time interval following launch. It remains thus unclear whether rosiglitazone per se may be hepatotoxic in very rare cases or not. What so ever, if anorexia, fatigue, abdominal pain, nausea, or jaundice occur with rosiglitazone (especially during the first few weeks after the initiation of treatment), it is wise to stop therapy with this agent and to monitor for hepatic dysfunction. Of course, rosiglitazone therapy should be discontinued immediately if liver enzyme levels become elevated.

■ LIVER TOXICITY AND PIOGLITAZONE

Well-controlled studies [review in 21, 84, 85] demonstrated that pioglitazone improves blood glucose profile of type 2 diabetic patients on diet alone [86] and of patients already receiving sulphonylurea [87], metformin [88] or insulin [21, 69]. Pioglitazone was approved by the FDA and commercialized in the US in July 1999. The European Agency for the Evaluation of Medicinal Products gave its approval in fall 2000 with the same limitations of use as for rosiglitazone [69].

Observations in clinical trials

Results from the US placebo-controlled study programme showed a total of 4 reports of elevated (≥ 3 × ULN) serum levels of ALT after pioglitazone treatment in 1 526 evaluable patients [89]. This 0.26% incidence was similar to that observed with placebo, as two of 793 placebo-treated patients (0.25%) had elevated serum ALT levels. The proportion of patients withdrawn from US clinical studies because of abnormal liver function test results was below 0.12% [21]. All patients with follow-up values had reversible elevations of ALT. No patient on pioglitazone had a ≥ 10 × ULN elevation in ALT compared with 12 patients (0.48%) on troglitazone *(Fig. 1)*.

The ALT issue in relation with fatty liver or NASH in patients with type 2 diabetes [26-28] is underscored by more detailed examination of what happened to patients in all pioglitazone trials who had elevations ≥ 3 × ULN [32]. There were 10 such patients; five had definite other causes and two were probably due to other drugs and indeterminate causes (in one the temporal relationship was unknown, in another there was a chronic elevation of alkaline phosphatase). So, it is not yet known if any hepatotoxicity occurs with pioglitazone.

Case reports of hepatotoxicity

Until now, no single case of severe liver toxicity has been reported with pioglitazone despite extensive use in the US since more than 18 months *(Fig. 2)*.

■ CONCLUSIONS

A crucial question is whether liver toxicity recently reported with troglitazone is related to all glitazones or whether it may spare rosiglitazone and pioglitazone, two other potent members of the TZD family commercialized in the US in 1999 and approved for use by the European Agency for the Evaluation of Medicinal Products in 2000. Even if no obvious hepatotoxicity has been demonstrated with these two compounds so far, careful monitoring of liver tests is recommended at least during the first year of therapy. However, the observations of a higher NASH-related prevalence of liver abnormalities in type 2 diabetic patients highlight the difficulty:

− in selecting diabetic patients which may safely receive glitazones as it is recommended to exclude patients with pre-treatment ALT > 2.5 × ULN;

− in interpreting minor elevations of ALT during treatment, especially when the three-times upper limit of normal threshold is used as a measure of liver toxicity. Current recommendations for the use of rosiglitazone or pioglitazone in type 2 diabetic patients are to control transaminase liver enzymes before initiating treatment, then every two months during the first year of therapy, and at periodic intervals afterwards. In case of ALT levels > 3 ULN, a new blood check must be performed rapidly, and the drug must be stopped immediatedly if such a high value is verified. Treatment with rosiglitazone or pioglitazone must also be interrupted in case of jaundnice.

In conclusion, several convincing arguments suggest that hepatoxicity reported with troglitazone, which led to the withdrawal of this compound from the market, is specifically related to the side chain of the molecule rather than to the common thiazolidine-2-4-dione structure shared by rosiglitazone or pioglitazone. While more long-term data are desirable, current clinical evidence thus supports the conclusion that severe hepatotoxicity is not a glitazone class effect.

REFERENCES

1 Bailey CJ. Insulin resistance and antidiabetic drugs. *Biochem Pharmacol,* 1999, *58,* 1511-1520.

2 Scheen AJ, Lefèbvre PJ. Oral antidiabetic agents: a guide to selection. *Drugs,* 1998, *55,* 225-236.

3 Scheen AJ, Lefèbvre PJ. Management of the obese diabetic patient. *Diabetes Rev,* 1999, *7,* 77-93.

4 Chen YDI, Reaven GM. Insulin resistance and atherosclerosis. *Diabetes Rev,* 1997, *5,* 331-342.

5 Scheen AJ. Drug treatment of non-insulin-dependent diabetes mellitus in the 1990s: achievements and future developments. *Drugs,* 1997, *54,* 355-368.

6 Grossman SL, Lessem J. Mechanisms and clinical effects of thiazolidinediones. *Exp Opin Invest Drugs,* 1997, *6,* 1025-1040.

7 Henry RR. Thiazolidinediones. *Endocrinol Metab Clin North Am,* 1997, *26,* 553-573.

8 Day C. Thiazolidinediones: a new class of antidiabetic drugs. *Diabetic Med,* 1999, *16,* 179-192.

9 Scheen AJ, Paquot N, Letiexhe MR, Lefèbvre PJ. Les thiazolidinediones. In:*Journées de Diabétologie de l'Hôtel-Dieu,* Flammarion, Médecine-Sciences, Paris, 1999, 213-229.

10 Schoonjans K, Auwerx J. Thiazolidinediones: an update. *Lancet,* 2000, *355,* 1008-1010.

11 Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes,* 1996, *45,* 1661-1669.

12 Spiegelman BM. PPAR-gamma adipogenic regulator and thiazolidinedione receptor. *Diabetes,* 1998, *47,* 507-514.

13 Spencer CM, Markham A. Troglitazone. *Drugs,* 1997, *54,* 89-101.

14 Chen C. Troglitazone: an antidiabetic agent. *Am J Health Syst Pharm,* 1998, *55,* 905-925.

15 Johnson MD, Campbell LK, Campbell RK. Troglitazone: review and assessment of its role in the treatment of patients with impaired glucose tolerance and diabetes mellitus. *Ann Pharmacother,* 1998, *32,* 337-348.

16 Plosker GL, Faulds D. Troglitazone. A review of its use in the management of type 2 diabetes mellitus. *Drugs,* 1999, *57,* 409-438.

17 Scheen AJ, Lefèbvre PJ. Troglitazone: antihyperglycemic activity and potential role in the treatment of type 2 diabetes. *Diabetes Care,* 1999, *22,* 1568-1577.

18 Campbell IW. Antidiabetic drugs present and future: will improving insulin resistance benefit cardiovascular risk in type 2 diabetes mellitus? *Drugs,* 2000, *60,* 1017-1028.

19 Fujiwara T, Horikoshi H. Troglitazone and related compounds. Therapeutic potential beyond diabetes. *Life Sci,* 2000, *67,* 2405-2416.

20 Balfour JA, Plosker GL. Rosiglitazone. *Drugs,* 1999, *57,* 921-930.

21 Gillies PS, Dunn CJ. Pioglitazone. *Drugs,* 2000, *60,* 333-343.

22 Watkins PB, Whitcomb RW. Hepatic dysfunction associated with troglitazone (letter). *N Engl J Med,* 1998, *338,* 916-917.

23 Kohlroser J, Mathai J, Reichheld J, *et al.* Hepatotoxicity due to troglitazone: report of two cases and review of adverse events reported to the United States Food and Drug Administration. *Am J Gastroenterol,* 2000, *95,* 272-276.

24 Dossing M, Sonne J. Drug-induced hepatic disorders: incidence, management and avoidance. *Drug Safety,* 1993, *9,* 441-449.

25 Lee WM. Drug-induced hepatotoxicity. *N Engl J Med,* 1995, *333,* 1118-1127.

26 Petrides AS. Liver disease and diabetes mellitus. *Diabetes Rev,* 1994, *2,* 2-18.

27 Luyckx FH, Lefèbvre PJ, Scheen AJ. Non-alcoholic steatohepatitis: association with obesity and insulin resistance, and influence of weight loss. *Diabetes Metab,* 2000, *26,* 98-106.

28 Nagore N, Scheuer PJ. The pathology of diabetic hepatitis. *J Pathol,* 1998, *156,* 155-160.

29 Benichou C. Criteria of drug-induced liver disorders: report of an international consensus meeting. *J Hepatol,* 1990, *11,* 272-276.

30 Jick SS, Stender M, Myers MW. Frequency of liver disease in type 2 diabetic patients treated with oral antidiabetic agents. *Diabetes Care,* 1999, *22,* 2067-2071.

31 Krentz AJ, Bailey CJ, Melander A. Thiazolidinediones for type 2 diabetes. *BMJ,* 2000, *321,* 252-253.

32 Tolman KG. Thiazolidinedione hepatotoxicity: a class effect? *Int J Clin Pract,* 2000 (Suppl 113), 29-34.

33 Scheen AJ. Hepatotoxicity with glitazones: is it a class effect? *Drug Safety,* 2001, in press.

34 Wise J. Diabetes drug withdrawn after reports of hepatic events. *Br Med J,* 1997, *315,* 1564.

35 Wageaar LJ, Kuck EM, Hoekstra JB. Troglitazone. Is it all over? *Neth J Med,* 1999, *55,* 4-12.

36 Bailey CJ. The rise and fall of troglitazone. *Diabetic Med,* 2000, *17,* 414-415.

37 Liver damage warnings for troglitazone. *Scrip,* 1997, *N° 2282,* 21.

38 Call to ban troglitazone in US. *Scrip,* 1998, *N° 2357,* 22.

39 Ault A. Troglitazone ban loses support. *Lancet,* 1999, *353,* 1161.

40 Food and Drug Administration. *FDA Talk paper*. Washington, DC: US Department of Health and Human Services; March 21, 2000.

41 Gitlin N. Julie NL, Spurr CL, *et al.* Two cases of severe clinical and histologic hepatotoxicity associated with troglitazone. *Ann Intern Med,* 1998, *129,* 36-38.

42 Neuschwander-Tetri BA, Isley WL, Oki JC, *et al.* Troglitazone-induced hepatic failure leading to liver transplantation. *Ann Intern Med,* 1998, *129,* 38-41.

43 Shibuya A, Watanabe M, Fujita Y, *et al.* An autopsy case of troglitazone-induced fulminant hepatitis. *Diabetes Care,* 1998, *21,* 2140-2143.

44 Vella A, de Groen PC, Dinneen SF. Fatal hepatotoxicity associated with troglitazone (letter). *Ann Intern Med,* 1998, *129,* 1080.

45 Neuschwander-Tetri BA, Isley WL, Oki JC. Troglitazone-associated hepatic failure (letter). *Ann Intern Med,* 1999, *130,* 330.

46 Herrine SK, Choudhary C. Severe hepatotoxicity associated with troglitazone (letter). *Ann Intern Med,* 1999, *130,* 163.

47 Misbin RI. Troglitazone-associated hepatic failure (letter). *Ann Intern Med,* 1999, *130,* 330.

48 Iwase M, Yamaguchi, M, Yoshinari M, *et al.* A Japanese case of liver dysfunction after 19 months of troglitazone treatment (letter). *Diabetes Care,* 1999, *22,* 1382-1384.

49 Jogannath S, Rai R. Rapid-onset subfulminant liver failure associated with troglitazone (letter). *Ann Intern Med,* 2000, *132,* 677.

50 Fukano M, Amano S, Sato J, *et al.* Subacute hepatic failure associated with a new antidiabetic agent, troglitazone: a case report with autopsy examination. *Hum Pathol,* 2000, *31,* 250-253.

51 Malik AH, Prasad P, Saboorian MH, *et al.* Hepatic injury due to troglitazone. *Dig Dis Sci,* 2000, *45,* 210-214.

52 Murphy EJ, Davern TJ, Shakil AO, *et al.* Troglitazone-induced fulminant hepatic failure. *Dig Dis Sci,* 2000, *45,* 549-553.

53 Schiano T, Dolehide K, Hart J, Baker AL. Severe but reversible hepatitis induced by troglitazone. *Dig Dis Sci,* 2000, *45,* 1039-1042.

54 Booth AM, Caldwell SH, Iezzoni JC. Troglitazone-associated hepatic failure. *Am J Gastroenterol,* 2000, *95,* 557-558.

55 Prendergast KA, Berg CL, Wisniewski R. Troglitazone-associated hepatotoxicity treated successfully with steroids (letter). *Ann Intern Med,* 2000, *133,* 751.

56 Arioglu E, Duncan-Morin J, Sebring N, *et al.* Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. *Ann Intern Med,* 2000, *133,* 263-274.

57 Kuramoto K, Shimizu N, Toda G. Liver dysfunction associated with troglitazone (Noscal) (in Japanese). *Rinsho Iyaku,* 1998, *14,* 461-466.

58 Ogata E, Yamada Y, Iga R. Liver dysfunction due to troglitazone (in Japanese). *Naika,* 1999, *83,* 534-539.

59 Toyota T, Ueno Y. Clinical effect and side effect of troglitazone (in Japanese). *Nipp Rinsho — Jap J Clin Med,* 2000, *58,* 376-382.

60 Riddle MC. Learning to use troglitazone. *Diabetes Care,* 1998, *21,* 1389-1390.

61 Imura H. A novel antidiabetic drug, troglitazone — reason for hope and concern (editorial). *N Engl J Med,* 1998, *338,* 908-909.

62 Zimmerman HJ, Ishak KG. Hepatic injury due to drugs and toxins. In: MacSween RNM, Anthony PP, Scheuer PJ, *et al.* (eds). *Pathology of the Liver* (3rd ed), London, UK, Churchill Livingstone, 1994, pp 563-633.

63 Inoue I, Katayama S, Takahashi K, *et al.* Troglitazone has a scavenging effect on reactive oxygen species. *Biochem Biophys Res Comm,* 1997, *235,* 113-116.

64 Guillouzo A, Morel F, Langouet S, *et al.* Use of hepatocyte cultures for the study of hepatotoxicity compounds. *Toxicology,* 1997, *82 (Suppl 1-3),* 209-219.

65 Kostrubsky VE, Sinclair JF, Ramachandran V, *et al.* The role of conjugation in hepatotoxicity of troglitazone in human and porcine hepatocyte cultures. *Drug Metab Disp,* 2000, *28,* 1192-1197.

66 Elcock FJ, Lyon JJ, Hitchcock J, *et al.* Toxicity of troglitazone in cultured rat hepatocytes (abstract). *Diabetes,* 1999, *48 (Suppl 1),* A63.

67 Galli EL, Crabb D. The role of hepatic peroxisome proliferator-activated receptors (PPARs) in health and disease. *Liver,* 2000, *20,* 191-199.

68 Marra F, Efsen E, Romanelli RG, *et al.* Ligands of peroxisome proliferator-activated receptor gamma modulate profibrinogenic and proinflammatory actions in hepatic stellate cells. *Gastroenterology,* 2000, *119,* 466-478.

69 Bailey CJ. Rosiglitazone and pioglitazone: two new thiazolidinediones. *Pract Diab Int,* 2000, *17,* 135-137.

70 Goldstein BJ. Rosiglitazone. *Int J Clin Pract,* 2000, *54,* 333-337.

71 Malinowski JM, Bolesta S. Rosiglitazone in the treatment of type 2 diabetes mellitus: a critical review. *Clin Ther,* 2000, *22,* 1151-1168.

72 Patel J, Anderson RJ, Rappaport EB. Rosiglitazone monotherapy improves glycaemic control in patients with type 2 diabetes: a twelve-week randomized, placebo controlled study. *Diabetes Obesity Metab,* 1999, *1,* 165-172.

73 Raskin P, Rappaport EB, Cole ST, *et al.* Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. *Diabetologia,* 2000, *43,* 278-284.

74 Nolan JJ, Jones NP, Patwardhan R, Deacon LF. Rosiglitazone taken once daily provides effective glycaemic control in patients with Type 2 diabetes mellitus. *Diabetic Med,* 2000, *17,* 287-294.

75 Wolffenbuttel BH, Gomis R, Squatrito S, *et al.* Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in type 2 diabetic patients. *Diabetic Med,* 2000, *17,* 40-47.

76 Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. *JAMA,* 2000, *283,* 1695-1702.

77 Salzman A, Patel J. Rosiglitazone is not associated with hepatotoxicity (abstract). *Diabetes,* 1999, *48 (Suppl 1),* A95.

78 Lebovitz HE, Salzman A. Rosiglitazone liver safety update (abstract). *Diabetes,* 2000, *49 (Suppl 1),* A39.

79 Jia DM, Tabaru A, Akiyama T, *et al.* Troglitazone prevents fatty changes of the liver in obese diabetic rats. *J Gastroenterol Hepatol,* 2000, *15,* 1183-1191.

80 Forman LM, Simmons DA, Diamond RH. Hepatic failure in a patient taking rosiglitazone. *Ann Intern Med,* 2000, *132,* 118-121.

81 AI-Salman J, Arjomand H, Kemp D, Mittal M. Hepatocellular injury in a patient receiving rosiglitazone. A case report. *Ann Intern Med,* 2000, *132,* 121-124.

82 Freid J, Everitt D, Boscia J. Rosiglitazone and hepatic failure (letter). *Ann Intern Med,* 2000, *132,* 164.

83 Isley WL, Oki JC. Rosiglitazone and liver failure. *Ann Intern Med,* 2000, *133,* 393-394.

84 New drug overview. Pioglitazone hydrochloride. *Am J Health Syst Pharm,* 2000, *57,* 124-125.

85 Schatz H, Massi-Benedetti M. (Eds). 2000. Pioglitazone: From discovery to clinical practice. *Exp Clin Endocrinol Diabetes, 108 (Suppl 2),* S221-S280.

86 Aronoff S, Rosenblatt S, Braithwaite S, *et al.* for The Pioglitazone 001 Study Group. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes. *Diabetes Care,* 2000, *23,* 1605-1611.

87 Kipnes MS, Krosnick A, Rendell MS, *et al.* Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in the treatment of patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med,* 2001, in press.

88 Einhorn D, *et al.* Pioglitazone hydrochloride in combination with metformin in the treatment of patients with type 2 diabetes mellitus: a randomized placebo-controlled study. *Clin Ther,* 2000, *22,* 1395-1409.

89 Rubin C, Schneider R. Pioglitazone liver enzyme profile is similar to placebo in US controlled clinical trials (abstract). *Diabetes,* 2000, *49 (Suppl 1),* A123.