Safety of PPAR Agonists

PHILIP HOME, DM, DPHIL

The thiazolidinediones pioglitazone and rosiglitazone were introduced into global markets in 1999–2000; we now have over 10 years of experience with them. The safety issues that it was fashionable to focus on at that time were abnormalities of liver function as a result of the rare but serious side effects of troglitazone, the thiazolidinedione then on the market. This turned out to be irrelavent for other thiazolidinediones without the antioxidant structure of troglitazone and has long since been forgotten in clinical practice.

Many practicing clinicians felt concern, however, with the mechanisms of action of these drugs, namely to influence gene expression (1). Although the chemical effects are quite specific, in terms of binding to peroxisome proliferator–activated receptors (PPARs), concern over unknown problems in longer-term use prevented their prescription by some. However, even at the time of marketing approval, the issue of fluid retention was a recognized problem of PPAR agonists as a class, and simple clinical logic implied that this might be an issue with regard to cardiac failure, leading to licensing cautions even at the time of approval (2–4). Troglitazone was already being investigated for preservation of β-cell function at that time, and a study set up to address the issue for rosiglitazone, A Diabetes Outcome Progression Trial (ADOPT), subsequently identified another safety issue—that of bone fractures in people taking thiazolidinediones (5). Before this, but receiving little attention, a suggestion appeared that rosiglitazone was associated with an adverse cardiovascular (CV) profile specifically in regard to myocardial ischemia, this becoming a headline issue after a later publication of an integrated trial-level analysis in *New England Journal of Medicine* (4,6) and resulting in a further regulatory review in the summer of 2010.

This article addresses four issues: *1*) evidence for genotoxicity with thiazolidinediones; *2*) our knowledge about increased fracture rates; *3*) the fluid retention, macular edema, heart failure issue; and *4*) CV safety, in particular, in regard to myocardial infarction (MI) for rosiglitazone.

RESEARCH DESIGN AND METHODS

—This article does not set out to be a systematic review of any of these areas. The literature in some of the areas is poor (genotoxicity, malignancy, and fracture rates); however, the literature on CV safety has been the subject of extensive ascertainment for the purpose of regulatory review and is well defined.

The author is a clinical trialist and believes in a hierarchy of evidence. Accordingly, randomized control trials (RCTs), in particular if double-blind, are taken as trumping other evidence, a view supported by clinical experience from other areas, in which many widely promoted clinical interventions have proven ineffective or harmful. However, epidemiological evidence can fill some of the voids left vacant by the absence of RCTs when broadly based or performed within the context of an RCT. Less useful are observational studies of prescribed drugs, largely because these are subject to hidden confounders. Confounding is usual because prescribers in a particular clinical circumstance may choose to use one drug rather than another, and those circumstances are usually not obvious to, nor ascertained by, the researcher. Lastly, pathophysiological evidence can play only a supportive role, its major function being to suggest further mechanistic and outcome studies in humans, or, where known a priori, to support the plausibility of a safety signal. Meta-analyses of any of these groups of studies can provide a useful function, but ultimately are only as good as the data that go into the original studies, and combining heterogeneous studies may introduce misleading bias not present in the original trials. A meta-analysis of RCTs, all of which have a similar defined outcome, can be useful if the original studies are underpowered, but meta-analysis of poor quality data will not improve them and may simply compound the uncertainty. Clinical expertise can be useful, provided it is based on published information as well as clinical experience, and provided it is not deviant from views of other authorities of similar competence. Many of these secondary studies, as well as clinical expertise, have an important role in hypothesis setting, but meanwhile can give rise to difficult regulatory issues.

Genotoxicity and malignancy

The chemical mechanism of binding of PPAR agonists to the PPAR receptor is well defined and known in molecular detail (1). It is a regulator of gene expression, and the gene(s) of major significance are involved in unknown ways in the regulation of fat metabolism, in particular, in peripheral adipose tissue. Indeed, it is not unreasonable to suggest that the major mechanism of action of PPAR-γ agonists is to promote fat deposition and decrease free fatty acid release in adipose tissue, thereby decreasing the fatty acid load to the liver and reducing the potential for lipotoxicity and inflammation in the liver, the islet β-cell, and indeed the endothelium, macrophages, and kidney. Although early studies suggest a range of activation of other genes in a variety of other tissues, where these have been identified, they are mainly concerned with metabolic effects and can be regarded either as secondary to the profound metabolic changes or as primary and consistent with regulation of lipid metabolism through the PPARs.

From the Newcastle University and Newcastle Diabetes Centre, Institute of Cellular Medicine (Diabetes), The Medical School, Newcastle upon Tyne, U.K.
Corresponding author: Philip Home, philip.home@ncl.ac.uk.
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In medical parlance, "genotoxicity" is often used as a synonym for oncogenicity. It is then worth considering the evidence for malignancy in the use of PPAR agonists.

Although some PPAR agonists have given adverse findings in malignancy toxicity studies in animals (at very high doses), there is nothing unusual in this in drug development; in diabetes, inhaled insulin and dipeptidyl peptidase-1 inhibitors have provided other examples. However, an exception is PPAR-α agonists (liver) and in particular PPAR-αγ agonists in regard to bladder neoplasms, a problem with more than one agent in rodents (7). Currently, new PPAR-αγ agonists are subject to particularly stringent and prolonged conditions for animal toxicological testing in this regard before prolonged exposure in humans.

It may well be that if this is an issue with PPAR-αγ agonists (as opposed to γ-agonists such as rosiglitazone), then it is growth promotion of tumors that is significant rather than genotoxicity. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, bladder malignancy rates were indeed possibly increased compared with control (placebo), although the effect was not sustained, in line with the suggestion of a growth promotion effect. However, the study was never powered to address this question, and thus the number of events was very small and conclusions must be guarded (8).

For rosiglitazone, the situation is clearer because of longer exposure in more patients in its CV outcome study, Rosiglitazone Evaluated for Cardiovascular Outcomes Regulation of Glycaemia in Diabetes (RECORD), and similar data being available from the ADOPT study. Furthermore, rosiglitazone is a pure PPAR-γ drug, and these drugs are not associated with bladder tumors in rodents. In RECORD and ADOPT, the malignancy rates are similar to those of metformin, a drug that if anything is believed to reduce the abnormally high malignancy rate of type 2 diabetes (9). Numerically, in both studies, malignancy rates were lower than for sulfonylureas, but this cannot be taken as conclusive, since numbers of events were too low to attain statistical significance in studies designed to answer different clinical questions.

In conclusion, whereas a small effect of PPAR-αγ agonists on bladder cancer cannot be excluded (and is not likely to be genotoxic), there is no reason to continue to hold the hypothesis that there is any other malignancy risk from current thiazolidinediones.

Increased fracture rate

An increase in fracture rate in people with diabetes treated with thiazolidinediones was not foreseen as a result of any of the toxicity studies in animals and was not picked up by any of the usual registration studies, even in aggregate, of the thiazolidinediones. The issue only became apparent as a result of careful pharmacovigilance monitoring by the sponsor of the ADOPT study, GlaxoSmithKline (GSK), added as a late addendum to the main ADOPT report (6). The problem was quickly confirmed by analysis of safety reports available to Takeda (manufacturers of pioglitazone) and GSK (10,11).

Following the hypothesis-setting observation in ADOPT, the RECORD study steering committee gave permission for analysis of fracture events in that study, though at the time ongoing. These events confirmed the ADOPT data, and indeed final RECORD results showed a doubling of fracture events in women, notably of distal lower limb and arm fractures (12). However, even RECORD, with large numbers of participants studied over several years, was not powerful enough to answer the question as to whether the lower background rate in men was also increased, the interaction *P* value being not statistically significant but the relative risks very different, and the trend consistent with observational studies (13).

Safety analysis of the PROactive study has compared the findings applied to pioglitazone as well as rosiglitazone, again with a doubling of fracture rate in women (8). Consistent with RECORD and ADOPT, this was true only for distal fractures, but the power of the study to detect changes in the rate of hip and spine fractures would be poor due to small numbers of such events. For these osteoporotic fractures, there were too few fractures in either PROactive or RECORD to reach any firm conclusion, but it is disturbing that there was a signal for an increase in both studies; this is consistent with animal data and signals from observational studies (13). A further important issue is that these studies are performed in relatively young populations (mean age around 60 years); will the relative risk (around ×2 in women) be maintained in the older age groups who already have much higher background rates?

Meanwhile, distal fractures remain, at around 1% per annum, the most clinically relevant side effect of thiazolidinediones. However, a problem arises with alternative therapies: insulin and sulfonylureas both carry a risk of falls due to hypoglycemia. Which medication class carries the higher fracture risk in the elderly?

Fluid retention, macular edema, and cardiac failure

As noted above, fluid retention was well recognized as a class effect of PPAR-γ medications at the time of licensing, to the extent that heart failure was a contraindication to use (2). Less adequately defined was whether development of any degree of fluid retention in someone with diabetes could precipitate heart failure and whether this might lead to significant morbidity or mortality.

The possibility that thiazolidinedione use is associated with macular edema was raised by a multiple case report in 2006, including a suggestion of partial resolution with cessation of the drug (14). As macular edema is not uncommon in people with type 2 diabetes, the clinical significance of the report remains uncertain. A substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) population could find no such association in patients using thiazolidinediones (mainly rosiglitazone) (15). Where alternative therapies are acceptable, it seems that thiazolidinediones should not be continued (or started) in people developing macular edema.

A randomized study with rosiglitazone in people with lesser degrees of controlled heart failure has been reported. In these people, followed for 12 months, worsened heart failure was unsurprisingly of high prevalence for both thiazolidinedione and control groups but doubled with rosiglitazone (16). Numbers of participants in the study were too low to properly judge whether secondary ischemic or mortality events were different between groups.

Curiously, heart failure was not a planned adjudicated outcome of the pioglitazone PROactive study, nor was it even a part of the primary or "principal" secondary outcome (8,17). After criticism that inclusion of heart failure events negated any positive improvement in the CV end points, post hoc adjudication of serious adverse events was performed, and an increase in heart failure was confirmed, albeit on a high background rate (18). The authors were unable to find any clear signal for an increase in further CV events, or death, in patients suffering heart failure on pioglitazone rather than "placebo", but background rates were already high in this secondary prevention study.

With a much lower background rate of heart failure, the RECORD study gives clearer data for rosiglitazone, studied in a typical general type 2 diabetic population rather than a high-risk population. Thus, even at the time of the forced interim analysis, heart failure (fatal or requiring hospitalization) was doubled by rosiglitazone compared with metformin/sulfonylurea, with the final hazard ratio (HR) being 2.10 and equivalent to an absolute increase in risk of ~1 per 400 patient-years (12). Deaths adjudicated as due to heart failure were also numerically increased, 10 vs. 2 over the ~12,000 patient-years of study in either arm, although this must be read in the context of there being 11 fewer CV deaths overall (including the heart failure deaths) in the rosiglitazone group.

The conclusion must be that heart failure is a clinically significant issue with thiazolidinediones. Fluid retention beyond modest ankle edema is an indication for stopping the drugs, as is any other cardiac compromise. Before starting these drugs, clinicians need to consider whether patients may have covert compromised cardiac function, for example, due to a previously significant MI, or if they have required diuretics for unknown reasons. In some people, echocardiography will then be indicated before such prescription.

MI

The first signal for a possible problem with rosiglitazone arose from a World Health Organization/Uppsala safety surveillance report in 2003, leading GSK to perform an integrated analysis of early studies, confirming the possibility of increased incidence in myocardial ischemia (19). A large observational study failed to confirm any problem for rosiglitazone compared with other glucose-lowering drugs (20). Although this information appeared in the public domain in September 2006, it only significantly influenced clinical practice as a result of a similar analysis of broadly the same group of papers by Nissen and Wolski in May 2007 (4,6). As noted above, meta-analyses are only as good as the data going into them, and in this case, the data remain poor, with low numbers of events (often zero) in short-term studies (mostly 6 months), from studies of heterogeneous aims and design, and including investigator-reported unadjudicated events only. It is generally agreed that such data can only be hypothesis setting.

Updated analyses (now of around 52 studies) have appeared recently, stimulated by regulatory review itself, stemming from the failure of the RECORD study to confirm such increased risk (see below). The most technically competent of these appears to be a patient-level analysis by U.S. Food and Drug Administration (FDA) statisticians of data supplied by GSK, giving an HR of 1.44 for the composite MACE end point (CV death, or hospitalization for MI or stroke) and 1.80 for MI, but the underlying data remain unreliable (21). A further issue here is that the signal appears only to be found in placebo-controlled studies, a situation of little relevance to diabetes care, and prompting unresolved questions as to why there should be a difference from active-controlled studies (22). Signals of higher risk in particular populations such of those using insulin in conjunction with rosiglitazone were based on weak data, and compounding of risk with use of other agents such as nitrates was not found in RECORD (12).

The early studies of pioglitazone did not suggest a problem of increased MI with this drug. However, these early studies with pioglitazone were on the whole of longer duration, and with a higher proportion actively controlled, than the early studies with rosiglitazone. This type of study did not show a problem for rosiglitazone. Although the PROactive study has its problems (heart failure not in the primary or principal secondary end point, open-label titration of other therapies in the placebo group, and nonsignificant difference from placebo for primary end point due to no effect on peripheral revascularizations, conducted entirely in a secondary prevention cohort), the consistency of reductions in the components of the statistically significant end point over 3 years seems sufficient to confirm some CV protection from this drug when compared with ill-defined investigator adjustment of other glucose-lowering agents (17). Attempts have been made to compare short-term studies of pioglitazone with those of rosiglitazone; however, these comparisons have little value, since the pioglitazone studies are much fewer in number, are generally against the active comparator, and are much longer in aggregate than the rosiglitazone studies (23).

The RECORD study was an open-label, 5.5-year randomized active comparator study of rosiglitazone against metformin or sulfonylurea (50% of each) (12). The primary outcome was a composite of CV hospitalization or CV death, perhaps inappropriately broad, since all vascular events were included and not just those of likely atherosclerotic origin. As RECORD was an open-label study, and as hospitalized CV events are diverse and often occur remote to the investigator site, events were carefully collected with recurrent and careful education and reminders to investigators, regular site visits by clinical monitors, and multiple methods of event capture (trial records, serious adverse event reports, and formal end point reporting), because data were handled by an independent contract research organization. Event adjudication was blind and by a committee of independent experts according to predefined definitions. Formal regulatory inspection by the FDA did not find significant issues (24). However, one FDA reviewer, working in isolation, without blinding, and with no predefined end point criteria, challenged some of the CV event ascertainment based mainly on serious adverse event reports rather than the formal event reporting/adjudication pathway. Therefore, RECORD is undertaking complete independent review of end points and serious adverse events.

The primary end point HR was very close to 1.00, with CIs sufficient to confirm noninferiority compared with traditional glucose-lowering agents (12). Many sensitivity analyses gave the same findings, including per-protocol analyses that are preferred by some authorities for noninferiority studies (24). The standard MACE end point (CV death, MI, and stroke) had a rather lower (better for rosiglitazone) HR at 0.93 (0.89 on randomized therapy).

Because of expressed concerns, some attention to secondary analyses is helpful (Table 1) (12,24). Heart failure is discussed above. Death, and in particular all-cause death (which is resistant to ascertainment bias), was numerically notably less on rosiglitazone treatment [HR 0.86 (95% CI 0.68–1.08)], implying that no adverse health risk, hidden or otherwise, could be giving rise to a clinically concerning mortality problem. However, results for MI itself were not by themselves completely reassuring, with the HR being 1.14, although MI is contained within the "safe" primary MACE end points. However, when other acute coronary events (unstable angina, hospitalization for acute angina, coronary revascularization) are included in MI events, central HRs decrease to

Table 1—*HRs and 95% CIs for the primary and secondary end points in the RECORD study, according to intention-to-treat and per-protocol analyses (12,22)*

	Intention-to-treat analysis			Dual therapy per-protocol analysis		
End point	HR (95% CI)	Rosiglitazone (*n*)	Metformin/ sulfonylurea (*n*)	HR (95% CI)	Rosiglitazone (*n*)	Metformin/ sulfonylurea (*n*)
Primary (CV death or CV hospitalization)	0.99 (0.85–1.16)	321	323	1.03 (0.86–1.23)	237	255
MACE	0.93 (0.74–1.15)	154	165	0.89 (0.68–1.17)	94	117
Myocardial infarction	1.14 (0.80–1.63)	64	56	1.18 (0.78–1.78)	47	44
Stroke	0.72 (0.49–1.06)	46	63	0.69 (0.45–1.08)	32	51
CV death	0.84 (0.59–1.18)	60	71	0.75 (0.44–1.27)	23	34
Heart failure	2.10 (1.35–3.27)	61	29	1.95 (1.16–3.29)	39	22
Total mortality	0.86 (0.68–1.08)	111	139	0.69 (0.44–1.11)	29	46

MACE, composite of CV death + MI + stroke.

0.96–1.05, making it difficult to sustain the view that rosiglitazone increases them. It remains possible that, after a first event, continuing on the drug could be associated with worse outcomes. Data from within the study are limited in that respect, but such as it is, there was no evidence of increased recurrent events or increased mortality (25).

RECORD has met with some criticism, mainly from individuals with previously expressed views against rosiglitazone. Issues of low event rate in this typical outpatient diabetes population (it is in line with other studies once adjustment is made for baseline risk), high rate of participant loss (<3% for vital status in 5.5 years), and poor drug adherence (88% exposure to rosiglitazone despite rescue algorithm stopping it when insulin started) do not hold up (24,26). As noted above, the study was open-label, but the outcome least subject to bias (all-cause mortality) gave one of the best central point estimates for rosiglitazone, with a low upper bound of the CI (Table 1).

In the context of an RCT such as RECORD, other types of study carry less weight in terms of the judgment of probability of safety. Nevertheless, the observational post hoc analyses within Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Veterans Affairs Diabetes Trial, Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetic Patients with Cardiovascular History (APPROACH), and Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI-2D) are all positive or neutral for rosiglitazone, and these complement RECORD by being performed in high-risk or very-high-risk people (27–29). These observational analyses have the advantage that the context of study is known, but even then, hidden confounding biases can operate, notably in what drives physician decisions to prescribe. This situation is much worse in other types of observational studies and studies using clinical care databases, where often little is known about prescribing context. In general, little notice is taken of studies with hazard (or odds) ratios of <1.5, and in that sense, the findings of the Medicare study in elderly patients are reassuring despite some signals of increased CV risk, particularly because the MI findings were not statistically significant and close to a HR of 1.00 (30). However, the ascertained data for people in these studies were for reasons unclear for a median of only 3.4 months, so the study has no real relevance to usual diabetes practice.

CONCLUSIONS—In most respects, use of thiazolidinediones in people with diabetes will be safe, provided attention is given to avoiding their use in people with a likelihood of left ventricular dysfunction and provided they are stopped in the event signs appear of significant fluid retention or macular edema. A more difficult issue is the increase in fractures, being a more common occurrence and one that may be difficult to predict. Although it seems wise to avoid the use of these drugs in anyone with conventional osteoporotic fracture risk factors (family history, previous falls, instability, some medical therapies), whether this is helpful is not known, and the risks of alternative therapies (such as insulin and sulfonylureas) needs to be considered in context. Overall, the CV safety of these medications looks reassuring, but regulatory review remains ongoing at the end of 2010, with suspension of marketing authorization of rosiglitazone in some countries and restriction in others. The readjudication of RECORD in 2011 is awaited with interest, and meanwhile there is controversy over the issue of regulatory review of glucose-lowering medication.

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