Review

Safety issues and prospects for future generations of PPAR modulators

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Abstract

Because of their wide range of actions on glucose homeostasis, lipid metabolism and vascular inflammation, peroxisome proliferator-activated receptors (PPARs) are promising targets for the development of new drugs for the treatment of metabolic disorders such as diabetes, dyslipidemia and atherosclerosis. In clinical practice, PPARα agonists, such as the already available fibrates, improve dyslipidemia, while PPARγ agonists, such as thiazolidinediones, improve insulin resistance and diabetes. The complementary action of simultaneous activation of each PPAR in patients suffering from metabolic syndrome and type 2 diabetes has led to new pharmacological strategies focused on the development of agonists targeting more than one receptor such as the dual PPARα/γ agonists. However, despite the proven benefits of targeting PPARs, safety concerns have recently led to late stage development failures of various PPAR agonists including novel specific PPARγ agonists and dual PPARα/γ agonists. These safety concerns include potential carcinogenicity in rodents, signs of myopathy and rhabdomyolysis, increase in plasma creatinine and homocysteine, weight gain, fluid retention, peripheral edema and potential increased risk of cardiac failure. Although the discontinued compounds shared common side effects, the reason for discontinuation was always compound specific and the toxicological or adverse effects which have motivated the discontinuation could be either due to the activation of PPARγ, PPARα or both (class effect) or due to a PPAR unrelated effect. Thus, the risk evaluation of each adverse effect should be viewed on a case by case basis considering both the PPAR profile of the drug, its absorption/distribution profile, the nature of the side effect and the putative PPAR-related mechanism of action. This review mainly focuses on the preclinical and clinical adverse events of PPAR agonists that could be of concern when considering the development of new PPAR agonists. The selective modulation of PPAR activities is a promising approach to develop new drugs with preserved efficacy but diminished adverse effects. © 2007 Elsevier B.V. All rights reserved.

Keywords: PPAR agonists; Safety issues; Side effects; Fluid retention; Edema; Congestive heart failure; Carcinogenesis; Myopathy; Rhabdomyolysis; Homocysteine; Creatinine, SPPARM

1. Introduction

Peroxisome proliferator-activated receptors (PPARs) are nuclear lipid-activated transcription factors that regulate the expression of genes involved in the control of lipid and lipoprotein metabolism, glucose homeostasis and inflammatory processes [13,14]. Their wide range of potential therapeutic actions make them attractive targets for the development of oral agents targeting risk factors associated with the metabolic syndrome, type 2 diabetes and cardiovascular diseases [15], and huge investments have been made in the last decade by several biopharmaceutical companies aiming to develop new PPAR activators with improved efficacy relative to the existing drugs.
The PPAR subfamily of nuclear receptors includes three isotypes, namely PPARα, PPARγ and PPARβ/δ which are encoded by three distinct genes. Each isotype displays distinct patterns of tissue distribution and has specific pharmacological activators [13]. All marketed PPARα agonists belong to the fibrate class. They are widely prescribed as hypolipidemic agents to reduce triglycerides while increasing plasma HDL-cholesterol [16]. Moreover, they reduce vascular inflammation and thrombogenicity [17]. The thiazolidinediones are oral anti-diabetic PPARγ agonists which have beneficial effects on glucose homeostasis by increasing insulin sensitivity and glucose disposal and prevent the loss of beta cell mass in the pancreas [18-21]. To date, no PPARβ/δ agonist has been fully developed and the clinical potential of targeting this isotype remains to be clearly determined. However, an increasing body of pharmacological studies suggests that PPARβ/δ activators can treat multiple aspects of the metabolic syndrome and type 2 diabetes, including visceral obesity, dyslipidemia, insulin resistance and vascular inflammation [22-24]. The recent results of the first phase Ia clinical trial with a PPARβ/δ agonist, GW501516, suggest that targeting this isotype may be a new approach for normalizing lipid levels in patients with mixed dyslipidemia.

Initial strategies aimed to develop new highly potent PPAR agonists specific for only one isotype. Accordingly, pure PPARγ agonists have been and/or are in development while, surprisingly, only few pure PPARα ligands are in the pipeline. However, combination therapy with drugs acting on different PPAR isotypes may have synergistic and wider therapeutic effects improving both glucose and lipid metabolism of patients suffering from metabolic syndrome and/or type 2 diabetes. Based on this hypothesis, new non-specific PPAR agonists (dual agonists and pan-PPAR agonists) are currently developed aiming to obtain synergism on lipid and glucose homeostasis from simultaneous activations of PPARα, PPARγ and/or PPARβ/δ (Fig. 1).

2. Development failures with PPAR agonists

Among the dual PPAR agonists, muraglitazar and tesaglitazar have elicited high hopes and have been evaluated in large scale phase III clinical trials in type 2 diabetic patients before recent discontinuation of their development [25]. As expected, they have demonstrated higher efficacy when compared to specific PPARγ agonists, simultaneously improving glucose and lipid homeostasis. Nevertheless, although these dual PPARα/γ agonists have demonstrated promising therapeutic activities, they were discontinued due to indications of safety concerns identified during phase II and phase III clinical trials (see Table 1). In addition to the well known glitazone-induced adverse effects on weight gain, fluid retention, hemodilution and edema, clinical trials with tesaglitazar or muraglitazar revealed side effects such as increase in serum creatinine and decrease in glomerular filtration rate (tesaglitazar) or increased risk of major cardiovascular events (muraglitazar [25]). In addition, other dual PPARα/γ agonists have been discontinued due to safety issues stemming from long term toxicology studies in animals (e.g. MK-767, ragaglitazar). Considering the high failure rate in the classes of PPAR targeting drugs, the FDA has reviewed toxicology data for more than forty PPAR agonist compounds. This extensive analysis highlighted several toxicological effects which might be associated with PPAR activation without providing any direct evidence of their human relevance. Nevertheless, considering the potential risk in clinical situations, the FDA emitted specific recommendations regarding the development of new PPAR modulators. Notably, the FDA ruled that 2-year carcinogenicity studies in rodents should be completed before beginning clinical trials of longer than 6 months duration with any PPAR agonist.

Except for muraglitazar, complete sets of data are not readily available concerning the undesirable side effects or toxic effects leading to development termination of failed PPAR agonists. Nevertheless, some results have been provided by the sponsor companies. Although most of the discontinued compounds shared some side effects, the reason for development discontinuation was always compound specific. Consequently, it is difficult to ascertain that the toxicological or adverse effects, which motivated their discontinuation were unequivocally due to the activation of PPARγ, PPARα or both (class effect) or due to a PPAR...
unrelated effect. Therefore, the risk evaluation of each adverse effect should be viewed on a case by case basis considering both the PPAR profile of the drug, its absorption/distribution profile, the nature of the side effect and the putative PPAR-related mechanism of action. In this review, we will mainly focus on the preclinical and clinical outcomes of developed or marketed PPAR agonists that can be of concern with respect to the long-term use of PPAR agonist in the treatment of chronic diseases.

3. Distinct PPAR activation profiles

As shown in Table 2, the selectivity ratio of the various PPAR agonists varies depending on the report and the in vitro test that has been used. However, it is noteworthy that none of the failed PPAR agonists were pure PPARα or PPARα-preferential dual agonists when tested on the human PPAR isoforms. Indeed, for most of the failed PPAR agonists, the apparent affinity for PPARγ is higher than the affinity for PPARα (see Table 2). Furthermore, these compounds should be viewed as full PPARγ agonists since they induce 100% of the transcriptional activity of the PPAR when compared to the reference compound rosiglitazone, while they behave as partial agonists on PPARα, inducing about 50% of the maximal activity seen with fenofibrate. Thus, all failed PPAR agonists to date are apparently pure PPARγ or PPARγ-preferential dual agonists. Consequently, although one cannot exclude cross-talk and synergistic toxic effects resulting from simultaneous actions on PPARα and PPARγ, most safety issues that led to development discontinuations are rather associated to over-activation of PPARγ than to action on the alpha isotype.

As extensively reviewed in the same issue of BBA, recent drug discovery studies have focused on identifying new non-TZD selective PPARγ modulators trying to minimize the side effects associated with the use of glitazones. These include metaglidasen (Metabolex), FMOC-Leu [26], nTZDpa [27], SPPARM12 [28], and the T131 molecule (Amgen (Tularik)). As exemplified in Fig. 2 for metaglidasen (the most advanced SPPARM presently in phase II/III), such ligands typically behave as partial agonists of the human form of PPARγ inducing about half of the maximal activity provoked by a saturating dose of rosiglitazone. Furthermore, SPPARγMs have a reduced ability to recruit specific cofactors and competitively block some rosiglitazone-mediated cofactor recruitment and transcriptional activity [26,28,29]. In agreement with the SPPARM concept, some of these compounds have already demonstrated pharmacological activity in various animal models of type 2 diabetes, without some of the side effects generally observed with full agonists ([27,28,30], metabolex). Therefore, in type 2 diabetic patients, metaglidasen is expected to have demonstrated anti-
### Table 1

**PPAR modulators (selective and dual PPARα/γ agonists) in clinical development (clinical phase II completed). Safety issues are mentioned when appropriate.**

<table>
<thead>
<tr>
<th>Compound name</th>
<th>Company (licensee)</th>
<th>Development status</th>
<th>Key Clinical trials</th>
<th>Clinical safety issues</th>
<th>Pre-clinical safety issues</th>
<th>Reasons for development discontinuation</th>
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<tbody>
<tr>
<td><strong>PPARα agonists</strong></td>
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<tr>
<td>Fenofibrate</td>
<td>Fournier Pharma</td>
<td>Launched</td>
<td>DAIS/LDS/FIELD</td>
<td>- Myopathy/Rhabdomyolysis</td>
<td>- Myopathy/Rhabdomyolysis</td>
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<td></td>
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<td>- Homocysteinemia</td>
<td>- Creatininemia</td>
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<td></td>
<td></td>
<td></td>
<td>- Lithogenicity</td>
<td>- Creatininemia (?)</td>
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<tr>
<td>Gemfibrozil</td>
<td>Pfizer Inc</td>
<td>Launched</td>
<td>LOCAT/HHS/VA-HIT</td>
<td>- Myopathy/Rhabdomyolysis</td>
<td>- Homocysteinemia (?)</td>
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<td></td>
<td></td>
<td>- Creatininemia</td>
<td>- Creatininemia (?)</td>
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<tr>
<td>Clofibrate</td>
<td>Launched</td>
<td>WHO</td>
<td>- Myopathy/Rhabdomyolysis</td>
<td>- Creatininemia</td>
<td>- Creatininemia</td>
<td></td>
</tr>
<tr>
<td>Bezafibrate</td>
<td>Roche Holding AG</td>
<td>Launched</td>
<td>BI/P/LEADER/SENDCAP/BECAIT</td>
<td>- Myopathy/Rhabdomyolysis</td>
<td>- Creatininemia</td>
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<td></td>
<td></td>
<td>- Homocysteinemia</td>
<td>- Creatininemia</td>
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<tr>
<td>Ciprofibrate</td>
<td>Sanofi-Aventis</td>
<td>Launched</td>
<td></td>
<td>- Myopathy/Rhabdomyolysis</td>
<td>- Creatininemia</td>
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<td><strong>PPARγ agonists</strong></td>
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<tr>
<td>Pioglitazone</td>
<td>Takeda Pharmaceutical (Eli Lilly)</td>
<td>Launched</td>
<td>PROactive/CHICAGO</td>
<td>- Fluid retention/Edema</td>
<td>- Weight gain</td>
<td>- Bladder tumor</td>
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<tr>
<td>Rosiglitazone</td>
<td>GlaxoSmithKline</td>
<td>Launched</td>
<td>DREAM/ADOPT</td>
<td>- Fluid retention/Edema</td>
<td>- Weight gain</td>
<td>- Liposarcoma</td>
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<tr>
<td>Rivoglitazone (CS-011)</td>
<td>Sankyo Co Ltd</td>
<td>Phase 3 clinical</td>
<td>Discontinued after phase 3 (2001)</td>
<td>- Weight gain</td>
<td>- Fluid retention/Edema</td>
<td>- Lack of efficacy?</td>
</tr>
<tr>
<td>Farglitazar</td>
<td>GlaxoSmithKline</td>
<td></td>
<td></td>
<td>- Lack of efficacy?</td>
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<tr>
<td>Metaglidasen (MBX-102)</td>
<td>Metabolon Inc</td>
<td>Phase 3 clinical</td>
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<tr>
<td><strong>PPARα/γ agonists</strong></td>
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<tr>
<td>Muraglitazar (Pargluva)</td>
<td>Bristol-Myers Squibb</td>
<td>Approved by FDA then Suspended (2006)</td>
<td></td>
<td></td>
<td>- Bladder tumor</td>
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<td></td>
<td></td>
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<td></td>
<td>- Weight gain</td>
<td>- Liposarcoma</td>
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<td></td>
<td></td>
<td></td>
<td>- Increased cardiovascular risks</td>
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<tr>
<td>Teraglitazar (Galida-AZ-242)</td>
<td>AstraZeneca plc</td>
<td>Discontinued after phase 3 (2006)</td>
<td></td>
<td>- Slight weight gain</td>
<td>- Increased serum creatinine and associated decreased glomerular filtration rate</td>
<td>- Increased serum creatinine and associated decreased glomerular filtration rate</td>
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<td></td>
<td></td>
<td></td>
<td>- Increase in serum creatinine</td>
<td>- Decrease in glomerular filtration rate</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>- Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regaglitazar (NovoNordisk)</td>
<td>Dr. Reddys Research Foundation</td>
<td>Discontinued during phase 3 (2003)</td>
<td></td>
<td>- Weight gain</td>
<td>- Anemia</td>
<td>- Urothelial cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Edema</td>
<td></td>
<td>- Tumors in mice and rats</td>
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<tr>
<td>Immunigluzar (TAK-559)</td>
<td>Takeda Pharmaceutical</td>
<td>Discontinued during phase 3 (2005)</td>
<td></td>
<td>- Findings of abnormalities in liver enzyme tests</td>
<td>- Findings of abnormalities in liver enzyme tests</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>- Lack of efficacy</td>
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</table>

diabetic activity while inducing less weight gain and decreased incidence of peripheral edema compared to currently used TZDs.

4. PPARγ mediated adverse effects

The thiazolidinediones (TZD) class of compounds, which includes rosiglitazone, pioglitazone (which are currently approved for the treatment of type 2 diabetes) and troglitazone (which was discontinued), have been the most studied. TZD PPARγ agonists are effective in ameliorating hyperglycemia in type 2 diabetes mellitus patients but their administration is associated with a number of adverse effects. These side effects have been categorized as either unique to individual TZDs, or common to the class of drug. Of the unique effects, the best characterized is hepatotoxicity, which has been associated to date specifically with troglitazone [31]. Studies with other glitazones indicate that hepatotoxicity is not a class effect [32]. Class side effects include body weight gain, hemodilution (decrease in hematocrit and hemoglobin) and peripheral edema, mild anemia and possible increased risk for congestive heart failure, which limits their clinical use.

4.1. Fluid retention, edema and risk of heart failure

TZD treatments are consistently accompanied by a modest but significant increase in body mass due to both an increase in adipose tissue and body fluid expansion. This fluid expansion is associated with hemodilution, peripheral edema and may thus potentially increase the risk of cardiac insufficiency. Thus, TZDs are contraindicated in patients at risk of cardiac failure [33] and fluid retention can be considered as the main limiting adverse event that should be avoided when developing new TZD-like drugs.

4.1.1. Fluid retention

In clinical practice, the anti-diabetic action of all TZDs as well as dual PPARα/γ agonists tested to date are paralleled by moderate decreases in hematocrit, red blood cell count and plasma hemoglobin [34–37]. At therapeutic doses, these side effects are classically associated with a hemodilution process resulting from fluid retention at the level of the kidney, although increased adiposity in the bone marrow has also been observed in toxicological studies in animals albeit at largely higher doses and plasma exposures (El Hage). As illustrated in Fig. 3 and discussed below, TZD-induced fluid retention might be the primary factor responsible for part of the weight gain, peripheral edema and potential increased risk of cardiac insufficiency.

 Despite recent reports focusing on the role of PPARγ in the modulation of Na+ transport in the urothelium, the underlying mechanism implicated in fluid retention seems to involve multiple factors/systems. Recently, in rodent models, two independent groups suggested an increased epithelial sodium channel (ENaC) activity and/or expression in the collecting duct as the main mechanism responsible for TZD-induced Na+ and fluid reabsorption. Indeed, in mice in which PPARγ was specifically invalidated in the collecting duct, TZD-induced body weight gain and plasma volume expansion was no longer observed in contrast to wild type mice, demonstrating a direct role of kidney PPARγ in this process [38,39]. According to these authors, fluid retention could be at least partially associated with TZD-induced expression of ENaCγ [39], but Chen et al. have shown that while the specific PPARγ agonist farglitazar increased sodium reabsorption at the distal nephron in the rat [40], this was not related to any change in the expression of the ENaC transporter subunits [40] or changes in renal filtration fraction [41]. These authors concluded that farglitazar increased sodium absorption in the distal nephron, probably by stimulating the ENaC and Na-K-ATPase system. However, they also reported that the direct inhibitor of ENaC, amiloride, failed to prevent but rather enhanced TZD-induced blood volume expansion suggesting that additional ENaC-independent mechanisms might be involved.

Although these animal studies establish a role for PPARγ and sodium transport in the TZD effect on Na+ and fluid retention, the relevance of these results are supported by the following

<table>
<thead>
<tr>
<th>Table 2</th>
<th>EC50 values (μM) and ratio of EC50 values (PPARα/PPARγ) of specific PPARα agonists and dual PPARα/γ agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EC50 alpha (μM)</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>18^a</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>61^b</td>
</tr>
<tr>
<td>Iberafibrate</td>
<td>14^b</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>41^e</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>4.3^b</td>
</tr>
<tr>
<td>Metaglidaen</td>
<td>11.9^b</td>
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<tr>
<td>4.1. Fluid retention, edema and risk of heart failure</td>
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<tr>
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</table>

Although these animal studies establish a role for PPARγ and sodium transport in the TZD effect on Na+ and fluid retention, the relevance of these results are supported by the following
4.1.2. Edema

Clinical experience shows that TZDs induce edema in 10–15% of patients [44–46], a percentage that increases upon combination treatment with insulin [47,48], sometimes requiring therapy discontinuation [49,50]. Although, TZDs do not increase arterial blood pressure, the plasma volume expansion resulting from fluid reabsorption in the kidney may lead to a luminal pressure rise in the microvasculature which increases the pressure gradient across the microvessel wall and the net rise in fluid flux towards the interstitial compartment. Furthermore, thiazolidinediones exhibit some properties of L-type calcium channel blockers [51,52] and may cause peripheral edema by similar mechanisms i.e. a decrease in arteriolar resistance that induces hydrostatic pressure in the precapillary circulation. Thus, the rise of an increased hydrostatic pressure gradient across the microvessel wall could be at least partially responsible for an increased fluid extravasation in the interstitial compartment and formation of peripheral edema.

Although TZDs consistently increase fluid extravasation, another hypothesis is that TZDs modify the intrinsic fluid permeability of the endothelial barrier. Several putative mechanisms can be proposed even though no study dealing with direct measurements of fluid flux across the endothelium has been published. TZDs have been shown to induce, probably via PPARγ activation [53], the expression of vascular endothelial growth factor (VEGF) [54–56], formerly shown to be a vascular permeability factor. Insulin itself has been demonstrated to contribute to peripheral edema risk [57] and improvement of insulin sensitivity by TZD treatment may cause edema by promoting insulin-mediated vasodilatation [58] and/or insulin induced endothelial permeability [59]. Nevertheless, Rennings et al. recently reported that the TZD-related fluid retention was not caused by improvement of the vascular actions of insulin, but suggested some relationships between the effects of rosiglitazone on glucose uptake and the interstitial fluid content [60]. Finally, numerous studies have demonstrated close links between PPARγ activation, the renin–angiotensin system, the release of endothelin-1 and nitric oxide in the vasculature all of which could collectively participate to TZD-induced vasodilatation and increased vascular permeability [61].

In conclusion, although the rise in luminal pressure in the microvessels is certainly linked to formation of peripheral edema, several additional mechanisms have been proposed suggesting direct actions of TZDs on the endothelium and subsequent increases in vascular permeability.

4.1.3. Risk of congestive heart failure

Together with previous clinical trials, the PROactive study, involving more than five thousand type 2 diabetic patients, argues for prevention from major cardiovascular events and deaths by TZDs. Although the study did not meet the primary endpoint, a combination of disease-related (mortality, non-fatal myocardial infarction, stroke and acute coronary syndrome) and procedural (coronary and leg revascularisation and leg amputation) endpoints, PROActive met its principal secondary endpoint, demonstrating that pioglitazone reduced the combined risk of heart attacks, stroke and death by 16% in high risk patients with type 2 diabetes [9].

Furthermore, a longitudinal study demonstrated that rosiglitazone prevents the development of type 2 diabetes in non-
diabetic patients suffering from insulin resistance and the metabolic syndrome (DREAM study [6]). Nevertheless, in both studies, the incidence of newly diagnosed cardiac insufficiency was higher in the TZD-treated group than in the placebo group and there remains a concern with regard to the propensity of these drugs to cause peripheral edema and to precipitate or exacerbate congestive heart failure (CHF) due to an increased cardiac workload resulting from plasma volume expansion [62]. Hence, although the TZD-associated edema is mainly restricted to the periphery and does not directly impair left ventricular function, subjects with class III or IV cardiac insufficiency (according to criteria of the New York Heart Association (NYHA)) were excluded from the clinical trials evaluating the safety and efficacy of both rosiglitazone and pioglitazone [33].

While several lines of evidence suggest that some patients can develop signs and symptoms of CHF upon TZD treatment, there appears to be no direct cardiac toxicity of these drugs. On the contrary, clinical studies in type 2 diabetics have demonstrated no troublesome effects on cardiac performance and there are even some trends toward improved function associated with long term TZD therapy [63,64]. Similarly, in a study carried out in diabetic patients with established heart failure, Tang et al. did not observe any direct association between fluid retention and the baseline degree of severity of heart failure [65]. In addition, the incidence rate of cardiac heart failure and patient hospitalization was found to be lower in patients treated with a glitazone than in patients treated with insulin, when the patients did not have congestive heart failure prior to treatment [66].

In agreement with the lack of any direct cardiac toxicity of TZDs, animal models consistently suggest that direct action of PPARγ on the heart could even be beneficial. Indeed, PPARγ agonists improve contractility and systolic performance [63,67,68], enhance diastolic performance [67,69] and decrease cardiac hypertrophy independent of loading conditions [70,72]. Other animal studies showed that TZDs may have beneficial effects on left ventricular remodeling and function after ischemic injury [73,74].

Thus, although TZD-induced fluid retention might increase the cardiac workload and subsequently increase the risk of cardiac insufficiency, all the published animal studies as well as clinical data to date support an overall cardioprotective effect of TZDs in type 2 diabetic patients. However, new PPAR agonists which do not increase fluid retention should be more cardioprotective than actual TZDs by limiting the potential risk of cardiac insufficiency and should be of great interest in the prevention of type 2 diabetes in patients suffering from insulin resistance and the metabolic syndrome.

4.2. Weight gain

Increases in body weight have been observed with all TZDs in all animal species including rodents and non-rodents as well
as in clinical trials [75,76]. Because body mass index is linked to insulin resistance and cardiovascular diseases, weight gain might be considered as a deleterious adverse event of TZD treatment in type 2 diabetics, many of whom are already overweight or obese. Although weight gain may occur upon TZD therapy, a weight-management program combining a low-calorie, low-sodium diet with education and behavior modification has been shown to be effective in patients treated with TZDs.

As discussed earlier, part of the weight gain may be ascribed to TZD-induced fluid retention, but these drugs are also associated with increased adipogenesis and fat redistribution. Indeed, several studies have shown that the weight gain may be correlated with an increase in subcutaneous adipose tissue and a concomitant decrease in visceral fat [77–79]. Due to the deleterious effects of visceral adipose tissue on insulin resistance and pro-inflammatory states, this change in fat distribution is generally considered as beneficial despite an overall increase in body fat mass [80]. A decrease in leptin levels and an increase in appetite have been seen with troglitazone treatment [81], but it is not clear whether the weight gain associated with rosiglitazone or pioglitazone can be attributed to this effect.

The main question regarding TZD-induced body weight gain is whether enhanced adipogenesis is necessary for the anti-diabetic effects. It is well known that activation of PPARγ provokes differentiation of pre-adipocytes into mature adipocytes. Furthermore, direct activation of PPARγ in mature adipocytes plays an important role in regulating lipid metabolism by increasing flux of fatty acids from the circulation and other peripheral tissues into adipocytes. Thus, part of the anti-diabetic action of TZDs could be due to adipogenesis, limiting the peripheral lipotoxicity that occurs in insulin resistant organs such as skeletal muscles. Alternatively, it is apparent that TZDs modulate the communication between adipose tissue, the liver and skeletal muscles. PPARγ activation induces adipocyte expression of the potent insulin-sensitizing factor adiponectin and concomitantly reduces the expression of several insulin resistance promoting polypeptides such as resistin, IL6 or TNFα. Furthermore, increased fat storage would be expected to enlarge adipocytes, but TZD treatment actually lead to smaller subcutaneous adipocytes. Interestingly, recent data suggest that new selective modulators of PPARγ are able to dissociate adipogenesis from insulin sensitizing effects, which is encouraging for the development of new anti-diabetic compounds with reduced weight gain [27].

4.3. Pro-carcinogenic effects of PPARγ

The effect of PPAR ligands on carcinogenesis is controversial. There are a number of preclinical in vivo studies suggesting that ligand activation of PPAR can potentiate tumorigenesis. The data are not equivocal and depend on numerous parameters such as the PPAR subtype, the animal model (rodent, non-rodent, non-human primate) and the cancer type (liver, colorectal, urinary tract, etc.). Further complicating this carcinogenesis issue is the fact that PPAR ligands often show anti-proliferation properties in large numbers of in vitro models [82]. The high prevalence of positive carcinogenicity findings with the PPAR agonists raises significant safety concerns for long-term clinical use. Therefore, before clinical trials can be conducted with compounds of this class, a 2-year rodent carcinogenicity study is required by the FDA.

Numerous studies have suggested that PPARγ or dual PPARα/γ activation can potentiate tumorigenesis [83–87]. Whether or not these effects are receptor-dependent or independent remain unclear. A review of the 2-year rodent carcinogenicity study data provided to the FDA for 11 PPAR agonists (5 γ agonists and 6 dual α/γ agonists) has revealed that these compounds are multi-species and multi-sex carcinogens (EL Hage, 2004 ww.w.fda.gov/cder/present/DIA2004/EHage, ppt). Thus, tumor types observed in rodents treated with PPAR agonists include: (A) transitional cell carcinomas of the urothelium obtained with 5 of the 6 dual PPARα/γ agonists and pioglitazone in all strains of rats (Sprague–Dawley, Fisher, Wistar), (B) hemangiosarcomas obtained with 8 of the 11 tested agonists (4 PPARγ agonists and 4 dual PPARα/γ agonists) in mice (CD-1 and B6C3F1) and hamsters (1 dual PPARα/γ agonist), (C) liposarcomas observed in rats with 3 PPARγ agonists and 3 dual PPARα/γ agonists and (D) sarcomatous tumors at multiple sites (muscle, skin, stomach, uterus and renal tubules) in rats or mice with dual PPARα/γ agonists (EL Hage, 2004). Mechanistic data to explain the mode of action involved in tumor development are still lacking.

Although it is possible that PPAR ligand-induced hemangiosarcoma only occurs in mice, studies are ongoing to better understand the mode of action. Based on the fact that the spectrum of tumor sites for PPAR-induced hemangiosarcomas overlaps with the location of extramedullary hematopoiesis, that PPARγ induces adiposity in bone marrow and that many tumors occur in the same animal species, the hypothesis is that bone marrow-derived cells, recently shown to play a critical role in tumor angiogenesis [88,89], may also play a role in the origin of hemangiosarcoma. Moreover, TZDs may increase neoangiogenesis by their action on endothelial progenitor cells (proliferation and augmentation of EPC functional capacity, prevention of apoptosis) [90] which may favor hemangiosarcoma formation. Recently, induced expression of the transcription factor Egr-1, phosphorylation of the transcription factor c-Jun and phosphorylation of the ribosomal S-protein have been suggested as a possible mechanism for the carcinogenic effect of MK-767 in rodents [91].

Regarding pioglitazone, ragaglitazar or muraglitazar-induced urothelial carcinogenesis, cellular hypertrophy is an early and primary change in the bladder urothelium [92], but no data are available to demonstrate whether it is a PPAR-dependent event. Another potential hypothesis implicates changes of urine composition resulting in the production of cytotoxic urinary solids that would induce regenerative proliferation and ultimately tumors. This effect, primarily observed in rats (not in mice), is much less likely to occur in primates, including humans [93].
From a conservative point of view, the human relevance of the tumor findings obtained in animal studies cannot be definitely ruled out since the tumors are observed in tissues which express PPAR receptors and since the tumor-induction potency appears to be correlated with PPAR agonist potency. Nevertheless it is noteworthy that even in rodents, the procarcinogenic effects of PPARγ as well as dual PPARα/γ are species-specific. Furthermore, although TZDs have been on the market for only a limited time, pioglitazone and rosiglitazone have now been prescribed to millions of patients in the US without any major alert regarding potential risk of carcinogenicity in humans. There is no evidence of any change in the number of malignant neoplasms in the longest clinical trials published to date: the PROactive and DREAM studies.

4.4. Other toxicological effects of PPARγ

4.4.1. Hepatotoxicity

As mentioned earlier, several clinical reports demonstrated liver toxicity in humans treated with troglitazone [94–96], often associated with significant elevations in serum alanine transaminase (ALT) [31]. Troglitazone appears to be the only thiazolidinedione which induces liver toxicity when compared to rosiglitazone and pioglitazone [31]. The mechanism of troglitazone-induced liver toxicity is poorly understood and may be PPARγ independent, especially considering that under normal circumstances, PPARγ is not expressed at functional levels in the liver.

4.4.2. Reproductive and developmental toxicity

The PPARγ receptor has been demonstrated to be essential for placental development since its disruption in rodents leads to embryo lethality [97,98]. As a consequence, it is expected that its activation during pregnancy could have effects on embryo development. The published reports on the potential developmental or reproductive toxicity induced by PPARγ ligands are rare. Animals studies performed with rosiglitazone and pioglitazone have shown no sign of altered development and the few analysis carried out in humans are consistent with these observations [99,100].

5. Potential adverse effects mediated by PPARα

To date, the best studied PPARα ligands are of the fibrate class (fenofibrate, gemfibrozil, bezafibrate, clofibrate, etc.). Fibrates have been used therapeutically for more than 30 years, and are well established effective agents for managing dyslipidemia, in particular elevated concentrations of triglyceride-rich lipoproteins (VLDL and VLDL remnants) and low levels of HDL-C that are typically associated with the mixed dyslipidemia characteristic of type 2 diabetes and the metabolic syndrome. Furthermore, their usefulness in the management of patients at risk for cardiovascular disease is further supported by several longitudinal clinical studies both in primary and secondary intervention settings (WHO, HHS, VA-HIT, BIP and FIELD). They are generally considered as safe drugs with only few side effects. Nevertheless, some adverse effects might be related to PPARα activation in humans including rare cases of myopathy and rhabdomyolysis, increase in creatinine and homocysteine, lithogenicity and gastro intestinal complaints. To date, no fibrate or other specific PPARα agonist has been withdrawn from the market or interrupted at late stage of development due to any of these side effects. However, such safety issues may become relevant when developing more potent PPARα agonists. Recently, the development of the dual PPARα/γ agonist tesaglitazar was suspended due to an unexpected increase in plasma creatinine levels.

5.1. Muscle toxicity and rhabdomyolysis

When used as monotherapy, fibrates including gemfibrozil [101–104], fenofibrate [105–108], clofibrate [109–111], ciprofibrate [112], and bezafibrate [113–114] may be associated with cases of muscle weakness and pain (myopathy) and extremely rare cases of rhabdomyolysis have also been reported [115]. Clinical signs of muscular toxicity parallel with increased serum creatinine phosphokinase (CPK) and histological studies show scattered muscle fiber necrosis [116]. It is noteworthy that, even used as monotherapy, all the fibrates would not have the same propensity to induce muscular toxicity in humans. The mechanism underlying fibrate-induced myopathy or rhabdomyolysis is still not well understood, and it is conceivable that the difference observed between fibrates results from their differential potencies in triggering the toxic mechanism. Fibrate-induced myotoxicity might rely on direct effects of PPARα activation in skeletal muscles, indirect effects resulting from exacerbated pharmacological activity or to PPARα independent effects. According to a PPARα dependent mechanism, it has been shown that severe myopathy in mice correlates with an increased expression of liprotein lipase, a well known PPARα target gene in skeletal muscle [117]. Similarly, Motojima et al. proposed that PPARα-mediated induction of pyruvate dehydrogenase kinase, isoenzyme 4 (PDK4) in the skeletal muscle and reduction of serum triglyceride levels as major energy source could cause protein degradation in muscles, leading to myopathy and ultimately to rhabdomyolysis [118,119]. Besides the mechanistic hypothesis, it has also been suggested that the differences in the propensity of fibrates to induce muscle toxicity could be related to the pharmacokinetic properties of each individual drug and that liver and kidney impairment are generally considered as important additional risk factors [120]. Whether of not PPARα is involved in fibrate-induced myopathy or rhabdomyolysis, it is important to keep in mind that the risk of myopathy associated with fibrate treatment is extremely rare (6 cases out of 10 000 patients [121] and no cases reported in the 10 000 patient cohort of the FIELD trial [77]), and to date, no fibrate or other new PPARα agonist has been withdrawn from the market or discontinued at late stages of development due to muscle toxicity.

In clinical practice, risk of myopathy and rhabdomyolysis may be increased when fibrates are prescribed as adjunct therapy in patients receiving statins [201]. Notably, in a post
marketing survey, cases of fatal rhabdomyolysis have been associated with co-prescriptions of gemfibrozil with cerivastatin [122] contributing to the withdrawal of cerivastatin from the market. Once again, clear differences can be observed between fibrates when used as adjunct therapy. Evaluating the differences in the rate of myotoxicity between the use of fenofibrate and gemfibrozil in combination with statins from the pharmacovigilance data collected by the FDA, Davidson and Jones reported that the use of fenofibrate in combination with a statin resulted in fewer reports of rhabdomyolysis than does the use of gemfibrozil [123]. This difference may be explained by the ability of gemfibrozil to interfere with the metabolism of certain statins. Indeed, it has been shown that gemfibrozil inhibits statin glucuronidation while fenofibrate does not [124].

5.2. Increase of plasma creatinine

In humans, a moderate and reversible rise in plasma creatinine levels is a common side effect of fibrates. This increased creatininemia has been reported in studies performed with fenofibrate [125–127], bezafibrate [126,128] and ciprofibrate [125,129]. The increased creatinine levels were observed in patients with normal as well as in those with impaired basal renal function, and in renal transplanted as well as in non-transplanted patients. The ability of gemfibrozil to increase creatininemia is extensively debated [130,131] and for some authors, gemfibrozil would present a better safety profile relative to fenofibrate or clofibrate in this respect [125,129]. It is unknown whether the effect on plasma creatinine results from a PPARα-related or unrelated effect. Several hypotheses have been proposed regarding the mechanism underlying fibrate-induced increase in serum creatinine. In their study, Broeders et al. reported a parallel increase in plasma urea leading to the hypothesis that the rise in creatininemia reflected an alteration of renal function [125]. Although direct evidence for a decrease in glomerular filtration rate upon fibrate therapy is still lacking, some authors propose that an altered renal function might be related to a PPARα-mediated down-regulation of cyclooxygenase (COX-2) in the kidneys [132] and resulting decreased synthesis of vasodilating prostaglandins [133]. In support of this hypothesis, clofibrate and ciprofibrate, but not gemfibrozil inhibited the production of vasodilatory prostaglandins [132,134]. Recently, the development of the dual PPARα/γ tesaglitazar has been discontinued presumably because the clinical trials showed elevations in serum creatinine and an associated decrease in glomerular filtration rate (http://www.astrazeneca.com/pressrelease - May 4 2006). For Lipscombe et al., the most plausible mechanism of the increase in serum creatinine is based on changes of renal hemodynamics. They propose that fibrates would induce natriuresis, leading to volume depletion and subsequently to increased urea and creatinine levels [130,135]. If true, the dual PPARα/γ agonist approach could be of great interest since the increase of sodium retention induced by PPARγ activation would counteract the diuretic effect mediated via PPARα. The hypothesis of Lipscombe was however challenged by Tsimihodimos et al. who argue that if this mechanism would be real, a disproportional increase in serum urea compared to serum creatinine would be expected [136] which has not been observed in most of the published studies [125,129]. Finally, the most recent reports suggest that fibrate-induced increase in serum creatinine does not reflect a deterioration in renal function since other more precise estimators of GFR remain unaffected [137,138]. The authors of these studies proposed that fibrate raise creatininemia by increasing net daily production of creatinine, presumably from muscle origin [138].

Although the role of PPARα activation in the mechanism of fibrate-induced rise in creatininemia remains to be clearly understood, the potential deleterious effects of some, but not all, fibrates on renal function suggest that their clinical use in patients at risk for renal insufficiency has to be carefully considered [133,139,140]. Nevertheless, considering the benefit/risk ratio, medical authorities recommend frequent assessment of plasma urea and creatinine levels in normal patients on fibrate treatment [125,126].

5.3. Increase of plasma homocysteine

Besides their effects on lipids, fenofibrate, ciprofibrate and bezafibrate consistently increase plasma homocysteine concentrations in dyslipidemic and diabetic patients [141–145]. There is some debate as to whether or not gemfibrozil increases homocysteinemia. In the secondary prevention VA-HIT study, gemfibrozil-treated patients exhibited an elevated homocysteine level vs. placebo [146]. Conversely, other authors claim that gemfibrozil is the only fibrate that does not induce this adverse effect [142]. At present, the underlying mechanism of fibrate-induced elevation of plasma homocysteine has not been extensively studied and no clear hypothesis has been provided. According to Dierkes et al., the most likely explanation for this increase in plasma homocysteine in humans would be an alteration of creatine–creatine metabolism [147]. Moreover, it is not clear whether this hyperhomocysteinemia is also dependent on folate status or renal function [147]. Numerous studies have reported that administration of folic acid alone or in combination with vitamins B12 and B6 generally normalize homocysteine levels in patients with hyper-homocysteinemia [148–154]. In contrast, co-administration of vitamins did not totally prevent the rise in plasma homocysteine provoked by fenofibrate [155–158], although the increase was significantly lower than that observed in patients treated with fenofibrate alone. Whatever the exact mechanism, and although there might be differences between various fibrates in increasing homocysteinemia in humans, the role of PPARα activation in this side effect is supported by an animal study performed in PPARα-deficient mice. In this study, the fenofibrate-induced increase in homocysteine observed in wild-type mice was not seen in PPARα-deficient mice [159].

Considering the efficacy/safety ratio of fibrates, it is important to note that the pathological significance of hyperhomocysteinemia remains a matter of discussion. According to a number of retrospective and prospective studies, hyperhomocysteinemia is consistently associated with an increased
risk of myocardial infarction, stroke and venous thromboembolism [160–162]. From a mechanistic point of view, this hypothesis is supported by a recent study demonstrating that plasma homocysteine could be pro-atherogenic through an inhibition of the reverse cholesterol transport process due to a decrease in plasma HDL. This effect of homocysteine on HDL particles could result from both an inhibition of ApoA1 synthesis, an increased HDL clearance [163] and an increased expression of Cyp7a1 [164]. However, in contrast, no prospective study to date has demonstrated that the reduction of plasma homocysteine by vitamin supplementation reduces the risk of developing major cardiovascular events. Very recently, the WAFTAS study (Women’s antioxidant and Folic Acid Cardiovascular Study) has shown no benefit of folic acid and B vitamins in high risk primary and secondary prevention of cardiovascular events [11]. Furthermore, the DAIS clinical trial (Diabetes Atherosclerosis Intervention Study) revealed that the fenofibrate-mediated increase in homocysteine levels did not attenuate the beneficial effect of fenofibrate on the prevention of atherosclerosis in diabetic patients. Therefore, whether hyperhomocysteinemia is a true cardiovascular risk factor or a marker of an existing cardiovascular disease remains debatable.

Interestingly, although hyperhomocysteinemia has been implicated as a causative factor in intimal hyperplasia development [165–167], PPAR-γ ligands have been described to reduce serum homocysteine levels in rodents and the associated intimal hyperplasia [168–170]. Consequently, because of the opposing actions of PPARα versus PPAR-γ agonists on homocysteine and intimal hyperplasia, the development of balanced dual PPARα/γ agonists may, once again, be of interest.

5.4. Lithogenicity

Humans treated with a PPARα agonist including clofibrate, bezafibrate or fenofibrate showed an increased risk for cholesterol gallstones [171,172]. By contrast, gemfibrozil appears less lithogenic compared to bezafibrate or clofibrate [173]. A possible mechanism underlying fibrate-induced lithogenicity could be the increased biliary output of cholesterol and the reduction of bile acid production via the PPARα-mediated downregulation of cholesterol 7alpha-hydroxylase (Cyp7a) and sterol 27-hydroxylase [174]. The involvement of PPARα activation in increased lithogenicity is suggested by the finding in mice that reduced bile output induced by ciprofibrate and bezafibrate requires a functional PPARα [174,175]. However, based on the relative ability of different PPARα ligands to cause cholelithiasis, other mechanisms contributing to this effect cannot be excluded.

5.5. Preclinical safety issues of PPARα agonists

5.5.1. Cardiac toxicity

The results of the VA-HIT and FIELD trials support the use of fibrates in the prevention of major cardiovascular events in type 2 diabetic patients. In the largest prospective study (FIELD) conducted in type 2 diabetes, although fenofibrate did not significantly reduce coronary heart disease mortality, a 24% reduction in risk of non-fatal myocardial infarction was observed. This was associated with a significant 21% reduction in the number of coronary revascularization procedures. Finally, a subgroup analysis showed that fenofibrate significantly reduced the total number of cardiovascular diseases in the primary prevention group but not in the secondary prevention group. The VA-HIT (Veterans Affairs HDL Intervention Trial) reported a 22% cardiac event reduction as well as a significant reduction in strokes. Despite these clinical results, it has been suggested that activation of PPARα could modify cardiac metabolism in a way that might be deleterious in patients with diabetic heart failure [176]. Accordingly, in animals, modulation of PPARα expression in the heart suggested a negative role of PPARα in the development of cardiomyopathy, due to a probable shift from glucose oxidation to fatty acid oxidation [177,178]. However, the importance of PPARα-induced beta-oxidation of free fatty acids as a potential cardiotoxicity mechanism is still controversial since it has been shown that PPARα activation by ciprofibrate did not induce any significant beta-oxidation in the heart [179], whereas other authors demonstrated that treatment with a strong PPARα agonist induced cardiomyocyte apoptosis preceded by enhanced myocardial beta-oxidation [180]. On the contrary, in diabetic models, treatment with a PPARα agonist does not aggravate the cardiac phenotype and may even reduce myocardial fatty acid oxidation [181]. Finally, when used as preventive treatments before ischemia/reperfusion injury in rodent models, PPARα agonists are cardioprotective, possibly due to their anti-inflammatory properties although other protective mechanisms may also be involved [182,183].

In conclusion, the fibrate class of drugs is rather cardioprotective. Nevertheless, it is noteworthy that results from clinical trials suggest differences between fenofibrate and gemfibrozil in the prevention of cardiovascular events, which may be related to their differential activities as selective PPARα modulators (see Table 2).

5.5.2. Hepatotoxicity and liver cancer in rodents

When administrated to rodents, fibrates produce a liver-specific response resulting in peroxisomal proliferation, hepatomegaly and ultimately hepatocellular carcinoma [184]. This effect has been demonstrated to be mediated by PPARα [175,185,186]. The magnitude of this response appears to vary considerably among species. In non-human primates and humans, PPARα agonists did not induce peroxisome proliferation nor the development of liver cancer [185,187]. In agreement, fibrates have been extensively prescribed for more than 30 years and an increased risk of liver cancer has never been reported in humans.

5.5.3. PPARα and other cancers

Some studies in rats have reported that alteration of PPARα expression and/or PPARα activation could induce carcinogenesis in other organs than liver (testis (Leydig cells), pancreas) [188]. These Leydig cell and pancreatic acinar cell tumors have
only been observed in rats but not in mice. Hypothetical mechanisms have been proposed which implicate PPARα ligand-induced Leydig cell and pancreatic acinar cell tumors via a PPARα-dependent pathway, but this has not been clearly demonstrated to date and the human relevance of these tumor responses are uncertain [188].

5.5.4. Reproductive and developmental toxicity

There are a limited number of studies which described reproductive or developmental toxicity of fibrates. It has been shown that administration of clofibrate or gemfibrozil to rats and mice during pregnancy could cause atypical changes in maternal and fetal liver that seem to be related to the rodent specific PPARα-induced phenomenon of peroxisome proliferation [189–191]. The dose required to cause these effects is considerably higher than those used therapeutically, and no evidence of overt fibrate-induced teratogenesis have been found [189,192,193].

6. PPARβ/δ potential adverse effects

While numerous studies have been performed to examine the effects of PPARα and PPARγ activation by specific ligands, the role of the third member of the PPAR family, PPARβ/δ, has not been extensively investigated until recently. As a consequence, less is known about the potential safety issues that could be associated to the use of PPARβ/δ-specific ligands. Conflicting results have been published regarding the role of PPARβ/δ in carcinogenesis. Intestinal tumorigenesis, but not colon carcinogenesis, is reported to increase in response to GW501516 in a genetically modified animal model [194]. However, other reports suggest that ligand activation of PPARβ/δ will inhibit colon carcinogenesis [195–197].

7. The future: selective PPAR modulators (SPPARMs)

PPAR agonists remain interesting drugs for the treatment of the risk factors associated with the metabolic syndrome and the prevention of type 2 diabetes, but they display certain side effects which limit their clinical development and therapeutic use. Current strategies aim at reducing side effects by identifying selective PPAR modulators (SPPARMs) and the optimization of the selectivity ratio between the different PPAR isoforms. These approaches should allow selection of new PPAR agonists with improved efficacy and/or safety profiles. An ideal selective PPAR modulator should result in the differential regulation of genes leading to beneficial effects on glucose and lipid homeostasis, without negative side effects. Although not unequivocally demonstrated, it is likely that the adverse effects result from high doses of full agonists, therefore partial PPAR agonism may be another approach to create an improved therapeutic window. Metaglidasen is the first insulin sensitizer, claimed to be a SPPARM, that is currently in phase III clinical trial. In June 2005, results from the phase II clinical trial were presented at the 65th ADA scientific sessions in San Diego showing that metaglidasen significantly improved metabolic parameters without the side effects of fluid retention/edema or weight gain. Other SPPARM molecules are currently in development including nTZDpa [27], SPPARM12 [28] and the T11 molecule (Amgen (Tulun)), and new SPPARMs are being increasingly synthesized. It is clear that the development of modulators which attain efficient therapeutic activity without PPAR related side effects will be important to fulfill unmet clinical needs in the treatment of metabolic disorders.

8. Conclusion

Numerous failures have questioned the feasibility of further PPAR agonist development for the treatment of metabolic disorders. This review has summarized the side effects associated with the clinical use of current PPAR agonists and suggests that the selective PPAR modulator concept is a valuable approach to develop new efficient PPAR agonists with limited side effects.

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