Peroxisome Proliferator-Activated Receptor γ Agonists and the Treatment of HIV-Associated Lipoatrophy: Unraveling the Molecular Mechanism of Their Shortcomings

Colleen Hadigan
National Institutes of Health, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland

(See the article by Mallon et al., on pages 1794–803.)

The recognition of metabolic complications associated with the use of antiretroviral therapy (ART), including dyslipidemia, lipoatrophy, and dysregulation of glucose homeostasis, followed close on the heels of the introduction and widespread use of potent combination ART for the treatment of HIV infection. Our understanding of the role of specific drug classes and of individual antiretroviral agents in these metabolic disturbances has evolved over time and has helped to inform clinical care practices to both prevent and treat these complications. In this issue of the Journal, Mallon et al. [1] present data that provide another important step forward in understanding the mechanisms of lipoatrophy in association with exposure to nucleoside reverse-transcriptase inhibitors (NRTIs) and offer insight into why treatment with the peroxisome proliferator-activated receptor γ (PPARγ) agonists has often failed to produce clinically significant gains in adipose tissue mass in trials involving HIV-associated lipoatrophy.

The potential role of mitochondrial toxicity associated with NRTIs, in particular the potent effects of thymidine analogues (tNRTIs), was recognized early in the study of lipodystrophy and ART toxicity [2] and subsequently confirmed in observational [3, 4], in vitro [5], and in vivo studies [6, 7]. The adipocyte transcription factor PPARγ was among the early targets of investigation in HIV lipodystrophy, given its known function in adipocyte cell differentiation, its preferential expression in subcutaneous adipose tissue, and the clinical overlap between HIV-associated lipoatrophy and genetic forms of lipodystrophy in which there are PPARγ gene defects. In 2003, Kannisto et al. [8] identified significant reductions in mRNA expression of PPARγ, as well as PPARγ coactivator 1 (PGC-1), an important regulator of mitochondrial biogenesis, in adipose tissue biopsy samples from HIV-infected patients with lipoatrophy, compared with samples from patients without clinical evidence of lipodystrophy. Subsequently, Mallon et al. [7] demonstrated reductions in PPARγ expression in adipose tissue biopsy samples obtained from HIV-negative, healthy volunteers after 2 weeks of exposure to dual NRTI therapy.

The building evidence implicating PPARγ in the mechanism of ART-related lipodystrophy paralleled clinical advances in HIV uninfected populations that demonstrated the potential benefits of PPARγ agonists for lipodystrophic diabetes. Arioglu et al. [9] showed improved insulin sensitivity and increased subcutaneous adipose tissue mass after 6 months of treatment with the PPARγ agonist troglitazone in an open-label study of patients with congenital and acquired forms of lipodystrophy. Combined, these observations supported future investigation of the utility of PPARγ agonists for treatment of HIV-associated lipoatrophy.

Since 2003, there have been 7 published reports of randomized trials of thiazolidinediones (6 rosiglitazone, 1 pioglitazone) to treat lipoatrophy in HIV-infected adults, with mixed results on improvements in subcutaneous adipose tissue mass [10–16]. Four studies found increased subcutaneous fat relative to a control arm, most often when measured in the lower limbs. Of note, in the trial by Slama et al. [16] the increase in leg fat with pioglitazone was only statistically significant in the subset of patients who were not on stavudine during the study. This observation was similar to those made previously by Carr et al. [12], who showed...
smaller increases in limb fat among patients who were receiving a tNRTI, relative to those who were not receiving a tNRTI. To more fully evaluate the mechanism for this observed disparity in response to a PPARγ agonist, Mallon et al. [1] report the results of a subcutaneous fat biopsy substudy conducted within the rosiglitazone trial of Carr et al. [12] in the current issue of the Journal. In this study, subcutaneous adipose biopsy samples were obtained from just over 40 HIV-infected, lipoatrophic participants at baseline and 2 weeks after randomization to receive either rosiglitazone (4 mg twice daily) or placebo, and follow-up biopsy samples after 48 weeks of randomized treatment were obtained from 28 subjects. These biopsy samples were assessed both for mitochondrial content and gene expression, as well as for mRNA expression of PPARγ, PGC-1α, and adipocyte fatty acid–binding protein (FABP4), important regulators of adipocyte differentiation and function.

Mallon et al. [1] make several clear and important observations in this work. First, they confirm that rosiglitazone therapy does not directly influence adipose mitochondrial gene expression or mitochondrial DNA content. Second, they show that 2 weeks of rosiglitazone increases PPARγ expression in patients not taking a tNRTI, but this effect is not observed in tNRTI-treated patients. And third, there was a significant positive correlation between increases in PPARγ expression and increases in limb fat, irrespective of treatment assignment or tNRTI use.

As in the original parent study, in the current report there was a tendency towards fewer patients receiving concurrent tNRTI treatment in the placebo arm (35% of patients were receiving tNRTIs in the placebo arm vs. 62% in the rosiglitazone arm), although these differences were not statistically significant. Given that the overwhelming majority, if not all, of these participants had past tNRTI exposure, with an average reported time to last exposure of 1.5 years, increases in PPARγ expression in the placebo-treated patients may simply represent ongoing restoration of expression following withdrawal of a tNRTI. This may, in part, also explain the increases seen in limb fat in the placebo-treated patients at 48 weeks in the original trial, especially in light of the observation that PPARγ expression rose in parallel with increases in limb fat in this substudy. Further, the continued use of a tNRTI was shown to inhibit rosiglitazone’s ability to increase PPARγ expression in adipose tissue, which helps to explain the observations made both by Carr et al. [12] and more recently by Slama et al. [16] identifying differential benefits with respect to limb fat with PPARγ agonist treatment, depending on concurrent use of a tNRTI.

So where does this leave us regarding the question of whether or not there is a role for PPARγ agonists in the treatment of HIV-associated lipoatrophy? The current work of Mallon et al. [1] helps shed light on the conflicting results observed in trials and supports the view that rosiglitazone lacks the capacity to increase subcutaneous adipose tissue mass in the context of ongoing tNRTI therapy. Although there have been more trials with positive results than with negative results, the amount of fat gained—even in those not using tNRTIs—has been relatively small. Furthermore, studies of antiretroviral switch strategies [17] and tNRTI-sparing regimens have demonstrated similar benefits without the potential toxicities associated with thiazolidinedione use, such as the lipid increases seen in most of the HIV trials that involved rosiglitazone. In the subset of HIV-infected patients with type 2 diabetes and lipodystrophy, pioglitazone may be an excellent choice of therapy given the potential beneficial effects on adipose tissue and more favorable effects on lipid profile, compared with rosiglitazone [16]. In summary, thiazolidinediones have fallen short of becoming the hoped-for corrective therapy for lipoatrophy in HIV, as have other tested treatments. The current work of Mallon et al. [1] helps broaden our understanding of the pathophysiology underlying lipoatrophy that accompanies NRTI use, and elucidates a mechanism that explains why PPARγ agonists do not completely reverse fat loss for many patients. Future investigation in this field, and in adipocyte biology in general, will hopefully bring us closer to effective strategies to prevent and reverse lipoatrophy in the management of HIV-infected patients.

References