Human Immunodeficiency Virus–Associated Lipoatrophy: Letting the Genome Out of the Bottle

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As effective as highly active antiretroviral therapy (HAART) has been in the management of human immunodeficiency virus (HIV) infection, the use of effective antiretroviral therapy has not been without adverse consequences. Yet, beneath the surface of apparent drug toxicities is a more complex set of factors that may contribute to these clinical conditions. In this issue of the journal, Hulgan et al. [1] shed light on the potential role that genetic polymorphisms may play in predisposing HIV-infected patients receiving HAART to lipoatrophy.

Since lipodystrophy was first described in 1998 [2], a number of studies have been published implicating antiretroviral therapy as its sole cause [3–6]. Initially, both fat atrophy and fat hyperplasia were thought to be manifestations of a single syndrome because they shared some common features. Subsequently, researchers found that although some antiretroviral agents were associated with each clinical syndrome, drugs in all classes were associated to some degree with lipoatrophy, and some protease inhibitors were associated with lipohypertrophy, suggesting that these clinical manifestations might be different, but related, syndromes.

A number of epidemiologic studies also demonstrated strong and consistent statistically significant associations between lipoatrophy and advanced HIV disease, white race, and male sex [7–10], although the biological explanation of these associations remained unclear. Furthermore, other studies demonstrated associations between lipoatrophy and tumor necrosis factor–α (TNF-α) gene promoter polymorphisms [11, 12]. In total, these studies suggest that both host and disease factors may contribute to this syndrome. Findings from a genomic analysis of HIV-infected persons, conducted by Hulgan et al. [1], have now provided a plausible biologic explanation for the contribution of some host factors to the onset of lipoatrophy. Whether there was some survival advantage in prehistoric times to individuals who carried the 187C/G polymorphism in the hemochromatosis gene (HFE) and mitochondrial haplotype J in northern latitudes where maintenance of subcutaneous fat was essential is an interesting subject on which to speculate. However, these polymorphisms may also be relevant in the development of or protection from lipoatrophy.

Mitochondrial toxicity has been hypothesized to be a major contributor to the development of lipoatrophy and of several other HIV-associated comorbidities, such as distal symmetrical polyneuropathy, anemia, pancreatitis, cardiomyopathy, and lactic acidosis [13]. The thymidine analogs have been primarily associated with the development of these clinical syndromes. The presumed mechanism has been drug-induced interference with the function of mitochondrial DNA polymerase–γ. Anderson et al. [13] have shown that intracellular levels of these drugs may be mediated by the chronic inflammation associated with HIV infection. These investigators found that the intracellular levels of the triphosphorylated moieties of the thymidine analogs were highest in patients with the lowest CD4+ T lymphocyte counts. Moreover, when these individuals were treated, the intracellular levels of the triphosphorylated drugs decreased as the CD4+ T lymphocyte count improved and the HIV load was suppressed [14]. Chronic inflammation has been hypothesized to be a mechanism because it was shown to increase phosphorylation of these drugs. Such a mechanism could explain why nucleoside analog–associated toxicities occur most commonly in the first 6 months after initiation of therapy. If these toxicities do not develop early in treat-
ment, when the intracellular levels of the drugs are high, they are far less likely to develop with continued exposure to thymidine analog treatment, when intracellular levels are lower [15]. When these toxicities are clinically manifest, treatment with the offending agent is discontinued. This same process may also be operative in the development of lipoatrophy. However, the difference between lipoatrophy and these other comorbidities may be that it takes many months to years to become clinically apparent, so the offending antiretroviral agent is often continued while the numbers of fat cells are subclinically decreasing. This creates the appearance of a “long-term” toxicity because a long duration of antiretroviral therapy seems to be associated with incident lipoatrophy, although in fact the pathologic event is acute but unrecognized clinically until much later. Although there is no feasible way to measure early, subclinical fat loss, the findings of Hulgan and colleagues suggest that we might to able to identify at-risk individuals and avoid use of offending agents. Patients who are not at risk would continue to have a broad choice of antiretroviral agents for treatment of their infection.

Similarities with factors associated with other nucleoside analog–associated toxicities also suggest that the chronic, uncontrolled inflammation associated with HIV infection and the subsequent elaboration of proinflammatory cytokines such as TNF-α, interleukin-1, interleukin-6, and interferon-γ may contribute to lipoatrophy as well. TNF-α has been found to be present in high levels in tissues involved in these nucleoside analog–associated adverse events, including adipose tissue.

Other studies have also looked quantitatively at the amount of mitochondrial material per cell and have demonstrated that HIV infection reduces cellular mitochondria levels whereas antiretroviral treatment, even with thymidine analogs, reconstitutes at least some of the mitochondria per cell [16]. In a study by Gallant and Deresinski [17], stavudine partially reconstituted the number of mitochondria per cell, whereas tenofovir brought the number of mitochondria per cell back to levels seen in uninfected individuals after 48 weeks of treatment. Such findings suggest that HIV infection, itself, is a contributor to mitochondrial dysfunction and that the drugs used to treat HIV infection have deleterious effects on the mitochondria and beneficial effects on the disease, but to different degrees.

Hulgan et al. [1] present yet another intriguing observation to explain mitochondrial dysfunction. They found that some individuals may be genetically predisposed to development of lipoatrophy, whereas others may be protected. Such a finding is consistent with epidemiologic studies and clinical trials that showed that a percentage of individuals receiving thymidine analogs did not develop lipoatrophy. Because their analysis addresses a genetic association among individuals who may either be predisposed to or protected from development of lipoatrophy, it provides evidence for the use of medications we might otherwise avoid giving to patients who may be genetically protected from the development of lipoatrophy. It also introduces another avenue of scientific inquiry in HIV disease and its many manifestations and complications.

The benefits of antiretroviral therapy are beyond question. These lifesaving drugs have changed the course of an otherwise fatal disease, enhanced quality of life, and provided hope for all HIV-infected individuals who have access to these medications. However, as our patients have responded to treatment, we have seen some of the adverse effects associated with that treatment. In some instances, however, we have been too quick to assign blame to these medications without taking into account the complex interplay between the drugs, the host, and the disease. We know which drugs are associated with specific toxicities. We also know that most of these toxicities occur more frequently in patients with more advanced HIV disease, that they occur early during the course of treatment, and that they do not occur in everyone. We have been comfortable studying the drugs and the relative differences between them because such clinical studies have been relatively simple to design, do not generally require basic-science laboratories, and have been supported by readily available funding from the pharmaceutical industry. This, I believe, has skewed our perceptions of antiretroviral therapy such that we have not paid sufficient attention to the underlying contributions brought about by HIV disease, chronic inflammation, and genetic predispositions, despite epidemiologic studies that have proven their strong associations with lipodystrophy and other untoward events. Hulgan and colleagues have begun to correct this by evaluating the genetic and pharmacogenomic processes that may contribute to the clinical syndromes that we attribute solely to antiretroviral agents. As we begin to understand such processes, we can more effectively select specific medications, medication combinations, and dosages that will bring about the best therapeutic outcomes with a minimum of adverse effects for our patients. We can avoid medications that may pharmacogenomically place an individual at risk and use them in individuals who may be protected. Such knowledge will permit us more options for therapy while we develop more-effective, better-tolerated agents.

References

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