Looking Beyond Highly Active Antiretroviral Therapy: Drug-Related Hepatotoxicity in Patients with Human Immunodeficiency Virus Infection

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Management of human immunodeficiency virus (HIV) has become increasingly complex since the introduction of highly active antiretroviral therapy (HAART). Patients with HIV have become exposed to an increasing array of drugs to treat HIV, prevent opportunistic infections and immune dysfunction, and manage comorbid illnesses and therapeutic complications. Hepatic complications have become common and may lead to discontinuation of treatment and significant morbidity. Up to 90% of patients with acquired immunodeficiency syndrome (AIDS) receive at least one drug that can cause hepatotoxicity. Clinicians treating patients with HIV frequently face difficulty distinguishing abnormal liver transaminase levels and toxicities in patients receiving several drugs. Some potential causes of hepatic dysfunction are viral infections, alcohol and substance abuse, and hepatotoxic drugs such as HAART. Recent reports have focused on the hepatotoxicity of HAART and the role of hepatitis viruses to the exclusion of many other agents prescribed for patients with HIV. Many of the common antibiotics, antifungals, antivirals, and ancillary agents prescribed for patients with HIV are independently associated with hepatotoxicity. Clinicians should be aware of the potential non–antiretroviral hepatotoxic agents that are frequently administered in HIV management.

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The introduction of highly active antiretroviral therapy (HAART) in the mid-1990s transformed acquired immunodeficiency syndrome (AIDS) from a progressively fatal disease complicated by opportunistic infections to a chronic one that is now often complicated by drug toxicities, resistance, and new comorbidities.[1] As patients infected with human immunodeficiency virus (HIV) live longer, comorbid illnesses such as viral hepatitis, tuberculosis, diabetes, hyperlipidemia, metabolic bone disease, and opportunistic infections have increased their exposure to a variety of pharmaceuticals beyond HAART. Many of these agents independently may cause liver injury, and some toxicities may be exacerbated by drug-drug interactions or comorbid liver diseases. Of the patients infected with HIV, 16% may be coinfected with hepatitis C, which may increase their risk of treatment-

related complications.[2, 3] Several recent articles have addressed the issue of the hepatotoxicity of HAART in patients with and without coinfection with hepatitis C virus.[3–13] Clinicians should be aware of other hepatotoxic drugs commonly administered to patients with HIV.

Transaminase levels 5 times higher than normal have been noted in 6% of asymptomatic patients with HIV.[3] Drug-related hepatotoxicity has been estimated to occur in up to 30% of patients with HIV treated with HAART.[4] However, the specific agents, actual frequency, and causal mechanisms associated with hepatotoxicity are difficult to assess from the literature due to a failure to use standardized definitions and reporting biases. Toxicity data from clinical trials may overstate asymptomatic, clinically irrelevant elevations in transaminase levels, whereas case reports are more biased toward reporting serious toxicities. With respect to HIV, newer observations regarding the mechanisms of HAART-related hepatotoxicity may negate some of the older reports of liver injury that predated these observations. With these caveats in mind, we attempted to review the hepatotoxicity of drugs other than HAART that are commonly administered to patients with HIV.

Methods

We performed a MEDLINE search of the literature published in English from January 1966–March 2002 on drug-related hepatotoxicity. Search terms were hepatotoxicity, hepatitis, liver toxicity, and the individual drugs (or drug classes) of interest. We narrowed the search to specific agents commonly administered to patients with HIV as recommended in clinical guidelines for management of HIV and opportunistic infections.[14, 15] Many agents we reviewed have been administered to patients without HIV, and many predated the administration of HAART. These reports were reviewed since they provided supportive data that associated the drug independently with hepatotoxicity in the absence of HIV and antiretroviral therapy. Whenever possible, we reviewed articles specifically about HIV-positive patients. Though other hepatotoxic pharmacologic agents are administered to patients with HIV, we limited our review to azole antifungals, anti-*Pneumocystis* agents, antituberculous agents, anti–*Mycobacterium avium* complex agents, anabolic steroids, antiherpes agents, anticytomegalovirus agents, and statins.

Most reports defined hepatotoxicity as a 3- to 5-fold increase from baseline in serum aminotransferase levels, with no known other precipitating cause, and with a return to normal after drug withdrawal. A few of these articles reported results of liver biopsy and/or drug rechallenge with the suspected agent. Ideally, reports of hepatotoxicity should characterize the type (hepatocellular, cholestatic, or mixed), the mechanism (direct cytotoxicity, hypersensitivity, immunologic, or mitochondrial toxicity), dose dependency, predictability, severity, and causality; however, these data frequently were absent from the reported literature. When they were available, we attempted to review the relationships of these variables with respect to drug class and specific agents.

Antifungal Agents

Fluconazole, ketoconazole, and itraconazole are azole antifungal agents commonly administered to patients with HIV to treat vaginal, oral, and esophageal candidiasis; dermatophyte infections; and systemic mycoses such as histoplasmosis, coccidioidomycosis, and cryptococcosis. The agents are generally well tolerated; side effects are primarily nausea, vomiting, and abdominal discomfort.

Prevalence

All three azoles can cause transient elevations in liver transaminase levels; ketoconazole is the most frequent offender.[16] One in 10,000–15,000 patients who receive ketoconazole may have a severe idiosyncratic liver reaction.[17] An estimated 2–10% of patients receiving ketoconazole experience asymptomatic increases in alanine aminotransferase and aspartate aminotransferase levels versus approximately 1–5% of those receiving fluconazole or itraconazole.[18]

Mechanism

All the azoles exert their antifungal effect by interacting with C-14α-demethylase, an enzyme dependent on cytochrome P450 (CYP), to inhibit ergosterol synthesis.[19] Similar interactions in mammalian cells with enzymes dependent on CYP may mediate some of the major toxic effects of the azoles (e.g., hepatotoxicity).[18] The observation that imidazoles, like ketoconazole, appear to be implicated more frequently than the

triazoles in causing liver damage may be due to their extensive liver metabolism and lower affinity for fungal rather than mammalian CYP enzymes.[20] Itraconazole, which also has extensive liver metabolism, more commonly causes abnormal transaminase levels than fluconazole.[21]

Though generally considered safe across a wide dosage range, fluconazole has caused significant hepatotoxicity. This may involve mild transient elevations in transaminase levels (1–3 times higher than normal), clinical hepatitis, cholestasis, fulminant liver failure, and even death.[17, 22–35] Most cases of significant liver injury related to fluconazole have occurred in severely immunocompromised patients (e.g., those with AIDS or a malignancy, or those who underwent transplantation), who frequently receive this drug.

Azole-associated elevations of transaminase levels tend to occur early in treatment, are usually reversible on discontinuation of the drug, and may recur on rechallenge.[26, 27] Acute hepatitis has developed as early as day 7 and as late as week 32 of therapy. Three patients with HIV who received fluconazole for cryptococcosis experienced early increases in liver enzyme levels, with a return to normal after discontinuation.[28] All three were rechallenged with fluconazole after 7–15 days without incident.

Fatal hepatic necrosis has been reported with fluconazole-induced hepatotoxicity in patients with AIDS.[17, 31–35] Furthermore, reversible subacute hepatitis characterized by a mixed hepatocellular and cholestatic pattern was reported in a patient with AIDS who was not receiving antiretrovirals and required prolonged fluconazole therapy for cryptococcosis.[32] Electron microscopy of the patient's liver biopsy revealed giant mitochondria with paracrystalline inclusions and enlarged smooth endoplasmic reticulum. These abnormalities resolved within 1 month after discontinuation of fluconazole. The authors suggested that liver injury during fluconazole treatment may be associated with hepatocyte mitochondrial disease in patients with AIDS. Many such cases were reported before administration of HAART or even multinucleoside agents for treatment of HIV.

Most of the initial reports of symptomatic hepatitis associated with ketoconazole have involved HIV-negative patients who were receiving treatment for resistant superficial dermatophyte infections.[36–42] Analysis of 33 patients with ketoconazole-induced liver injury found biochemical evidence of hepatocellular or mixed liver injury that developed 1.5–24 weeks after ketoconazole therapy was begun; median onset of clinical illness was 4 weeks.[36] Abnormal laboratory values persisted up to 7 weeks after discontinuation of therapy. Commonly reported manifestations of ketoconazole-induced liver toxicity are jaundice (up to 50% of patients) and anorexia, malaise, nausea, and vomiting (one third of patients).[16] Rechallenge usually results in recurrent hepatitis, with symptoms identical to those of the initial episode. Ketoconazole also has been associated with death from acute hepatic necrosis.[36, 39–42]

Itraconazole frequently is better tolerated than ketoconazole; however, it also may cause hepatic dysfunction. The frequency of reversible symptomatic acute hepatitis secondary to itraconazole is increased with higher dosages and prolonged therapy.[43] The pattern of abnormal laboratory values and clinical symptoms of acute hepatitis begin within 5–6 weeks after itraconazole therapy is begun, and is similar to the pattern that occurs with ketoconazole hepatotoxicity. Laboratory values return to normal approximately 8–10 weeks after discontinuation of the drug.[43, 44]

The newest azole, voriconazole, is a triazole with enhanced activity against *Candida* as well as *Aspergillus* organisms. It undergoes extensive hepatic metabolism. The first of two recent large studies of voriconazole efficacy and safety compared voriconazole with liposomal amphotericin B in patients with neutropenia and persistent fever.[45] In the voriconazole group, 9% had abnormal transaminase levels, which was comparable to those in the amphotericin B group.[45] The second study evaluated voriconazole in 137 patients with acute invasive aspergillosis (4% of whom were HIV positive).[46] Increases in transaminase levels were significant in 14% of patients, but alterations in therapy were not required. One third of the patients with abnormal liver test results had very high blood levels of voriconazole.

Macrolides

Erythromycin, the most widely prescribed macrolide, is associated with cholestatic liver injury in 3.6/100,000 doses and usually occurs 1–3 weeks after administration.[16] It is administered infrequently to patients with HIV. However, azithromycin and clarithromycin are expanded-spectrum macrolides frequently given

for treatment of respiratory tract infections and for prophylaxis and treatment of *M. avium* complex infection and disease in patients with HIV. In early clinical trials in patients without HIV, less than 1% of patients treated with clarithromycin experienced elevations in alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, and total bilirubin levels.[47] Elevations in transaminase and alkaline phosphatase levels (more than 5 times the upper limit of normal) were observed in up to 4% of patients with HIV who were participating in manufacturer-sponsored clinical trials.

Postmarketing adverse events with clarithromycin are hepatic dysfunction with increased transaminase levels and cholestatic hepatitis with or without jaundice.[48] Hepatotoxicity may be dose related, especially in elderly patients.[49] Hepatic dysfunction, although rare, may be severe and is usually reversible on discontinuation of the drug. One case of severe hepatocellular injury requiring liver transplantation occurred in an otherwise healthy 25-year-old man who was receiving clarithromycin.[50] A study of clarithromycin for treatment of disseminated *M. avium* infection in patients with late-stage HIV reported abnormal transaminase levels as the most common adverse effect. This occurred in 26% of patients, of whom 5% required discontinuation of clarithromycin and 8% required dosage modification.[51]

Because of simple once-weekly dosing, azithromycin has become the preferred agent for *M. avium* complex prophylaxis for patients with AIDS. Though the 1200-mg dose administered for prophylaxis is commonly associated with nausea, vomiting, and diarrhea, hepatic dysfunction is rare. The frequency of cholestatic jaundice was 1% or less in premarketing trials of azithromycin. The frequency of abnormal laboratory findings (increased levels of alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase) reported during clinical trials with azithromycin was 1–2%.[52] Postmarketing information contains infrequent reports of hepatitis and cholestatic jaundice.

Antituberculosis Agents

During the 1980s and 1990s, a resurgence of tuberculosis occurred in the United States, affecting primarily patients with HIV.[53] In addition to increasing the risk of developing active tuberculosis, AIDS may predispose to the development of serious hepatotoxicity during treatment with antituberculosis agents.[54, 55] Isoniazid, rifampin, and pyrazinamide—the first-line antituberculosis drugs—are effective but are associated with an increased frequency of adverse reactions, which limits their administration. Isoniazid may cause hepatocellular injury. Liver toxicity was reported in 3% of patients treated with rifampin and isoniazid in the United States[56] and in 4% of patients treated with rifampin and isoniazid with or without pyrazinamide in the United Kingdom in the pre-HIV era.[57]

In most cases, elevations in liver enzyme levels due to antituberculosis drugs are mild and resolve without treatment modification. However, the frequency of all adverse reactions to antituberculosis agents prescribed for patients with HIV in the United States and the United Kingdom is much higher and varies from 4–18%.[58, 59] The relative risk of drug-induced hepatotoxicity in patients infected with the hepatitis C virus or HIV is increased 5 and 4 times, respectively, and 14 times in those coinfected with both viruses.[55] Frequent monitoring is recommended for all patients with HIV who are receiving antituberculosis therapy, especially when several risk factors for development of hepatotoxicity are present (age > 35 yrs, concomitant alcohol consumption, and chronic liver disease).[60, 61]

Direct cytotoxicity (by the drug or its metabolites) is the most likely mechanism of drug-induced hepatotoxicity from antituberculosis drugs. An immune-related component is believed to coexist, as both isoniazid and rifampin have documented immunologic effects.[55] Histopathologic findings may range from spotty to diffuse necrosis with partial to complete cholestasis. Chronic active hepatitis may develop in up to 10% of patients with isoniazid-induced hepatotoxicity who show degenerative changes of the periportal space as well as inflammation and fibrosis.[62] Rifampin is the only antituberculosis agent that can inhibit both the uptake and excretion of bilirubin in a dose-related manner. As a result, patients may experience jaundice from elevated plasma levels of both conjugated and unconjugated bilirubin.

Rifampin alone seldom causes hepatitis. The mechanism of this liver injury is unknown but is unpredictable and not dose related.[62] Pyrazinamide is a synthetic analog of nicotinamide, which is bactericidal against intracellular mycobacteria. At one time pyrazinamide was given at a dosage of 40–50 mg/kg/day and was responsible for

many cases of acute hepatitis, some of which were fatal.[63] Since the recommended dosage has been decreased, hepatotoxicity has been reduced substantially and is generally mild.[63] In a large series of cases, the addition of pyrazinamide 25–40 mg/kg/day to regimens containing rifampin and isoniazid did not increase the frequency of hepatitis.[57]

In an effort to control the resurgence of tuberculosis in the United States, the Centers for Disease Control and Prevention (CDC) recommended prophylaxis in purified protein derivative skin test converters of all ages who are at risk for activation of tuberculosis.[64] The preferred regimens for isoniazid-susceptible strains of tuberculosis are isoniazid (either 300 mg/day or 900 mg twice/wk) for 9 months, or rifampin 600 mg/day plus pyrazinamide 20 mg/kg/day for 2 months. The risk of isoniazid-induced hepatotoxicity during treatment of latent tuberculosis infection is thought to be 5–20 cases/1000 patients treated, with a case-fatality rate of 1–10%.[65] These estimates are based on studies conducted more than 20 years ago, when the diagnosis of isoniazid-induced hepatotoxicity was made on the basis of only mild elevations in transaminase levels.[65] More recent studies have shown that administration of isoniazid for treatment of latent tuberculosis infection is generally safe and well tolerated, regardless of age, when symptoms and liver enzymes are monitored monthly.[66] A large prospective cohort study found that although the rate of hepatotoxic reactions during isoniazid preventive therapy increased with age, the overall risk was much lower than previously recorded (0.10–0.15% vs 2–3%).[65]

The regimen of rifampin plus pyrazinamide for 2 months is a valuable alternative for isoniazid-resistant strains of tuberculosis for patients who experienced previous adverse reactions to isoniazid, or when patient adherence to a longer regimen could be unreliable. The efficacy and safety of this regimen has been demonstrated in patients with HIV.[67–69] However, 23 cases of severe and fatal liver injuries associated with the rifampin-pyrazinamide regimen among patients not infected with HIV were reported to the CDC from February–August 2001. As a consequence, the American Thoracic Society and the CDC, with the endorsement of the Infectious Diseases Society of America, revised their recommendations.[70] They propose that for treatment of latent tuberculosis infection, the 9-month isoniazid regimen is still preferred, regardless of HIV status; rifampin administered daily for 4 months is an acceptable alternative. Rifampin-pyrazinamide should be administered daily for 2 months only with caution and only when the patient can be monitored closely throughout the course of treatment.

Rifabutin, a derivative of rifamycin S, is as effective against *M. tuberculosis* as rifampin.[71] Furthermore, rifabutin has lower minimum inhibitory concentrations than those of rifampin against *M. avium* complex isolates,[72] and it is a less potent inducer of the CYP enzyme system.[73] Therefore, rifabutin could be administered for treatment of tuberculosis or for prophylaxis or treatment of *M. avium* complex in patients with HIV who are receiving HAART.

Rifabutin appears to be well tolerated at a dosage of 300 mg/day in patients with HIV[73] and up to 450 mg/day in HIV-negative patients.[74] No significant liver toxicity was reported with rifabutin administration in these patients.[73, 74] However, the combination of rifabutin and clarithromycin seems to increase the possibility of clinically significant hepatotoxicity.[75] In one small study, abnormal liver enzyme levels developed in 12% of patients with HIV who were receiving both drugs; one third of these patients required adjustment of therapy.[75] Dosage adjustment or drug level monitoring may be necessary for patients receiving concomitant rifabutin and HAART.

Anti-*Pneumocystis* Agents

Four agents commonly administered for prevention and treatment of *Pneumocystis jiroveci* pneumonia in patients with AIDS are trimethoprim-sulfamethoxazole (TMP-SMX), pentamidine, dapsone, and atovaquone. Trimethoprim-sulfamethoxazole is commonly prescribed for a wide variety of infections. In patients with HIV, this combination antibiotic often is given to treat acute episodes of *P. jiroveci* pneumonia, or as prophylaxis in patients whose $CD4^+$ cell count is less than 200/mm^3 (or < 14% of the lymphocytes) or who have thrush or unexplained fevers.

Liver injury induced by TMP-SMX is rare and is characterized by a mixed hepatocellular-cholestatic pattern. Symptoms of hepatocellular necrosis can develop quickly after the start of TMP-SMX therapy (a few hrs–10 days) and are considered a hypersensitivity reaction.[76] Cases of severe hepatocellular injury resulting in death have been reported.[77] A less severe, primarily

cholestatic reaction appears reversible on discontinuation of the antibiotic. Symptoms develop an average of 2.5 weeks after onset of TMP-SMX therapy (ranging a few days to 1 mo). Although the symptoms usually resolve within 6 months, pruritus and abnormal liver function tests can persist for up to 2 years after discontinuation of the agent.[78] Liver biopsy reveals a centrilobular pattern with minimal inflammation. Inadvertent rechallenge has resulted in repeated episodes of acute cholestatic hepatitis.[79]

Given the high frequency with which TMP-SMX is prescribed worldwide, the rarity of well-documented cases of liver damage suspected to be induced by this compound is surprising. A large population-based study in the United Kingdom revealed that 5.2/100,000 patients risk developing clinically important liver disease after receiving a course of TMP-SMX.[80] Furthermore, in a 10-year span in Denmark, only 23 cases of liver disease induced by TMP-SMX were reported.[81] However, early in the AIDS epidemic it became clear that frequency of hepatic damage is substantially higher due to TMP-SMX,[82–86] with hepatotoxicity observed in approximately 20% of patients taking the compound. The cause of this increase in toxicity is unclear but has been postulated to be associated with inability to clear a hepatotoxic metabolite, sulfamethoxazole hydroxylamine.[87]

Intravenous pentamidine is given as an alternative treatment of moderate-to-severe *P. jiroveci*. Prospective studies have reported treatment-limiting toxicity with pentamidine in 13–80% of patients.[86] Liver toxicity seems to be less common and less severe than with TMP-SMX but developed in 15% of patients in one study.[88] None of the patients required discontinuation or reduced dosage of pentamidine. The drug's most common side effects are nephrotoxicity and hypoglycemia, but liver function abnormalities, though frequent, usually are of little consequence. Few data are available regarding risk of inhaled pentamidine for treatment of *P. jiroveci* prophylaxis. In one trial, incidence of elevated transaminase levels was 1.7% for pentamidine in aerosol form versus 12.2% for oral TMP-SMX.[89]

Dapsone is a sulfone antiinfective administered for both treatment and prophylaxis of *P. jiroveci* in patients with HIV who cannot tolerate TMP-SMX. Some adverse reactions are dose-related hemolytic anemia and methemoglobinemia, which are most severe in patients with glucose-6-phosphate dehydrogenase deficiency. The frequency of dapsone-induced adverse events is increased in patients treated with dapsone and trimethoprim in combination, probably due to higher dapsone serum concentrations.[90] Transient elevations in transaminase levels typically occur within the first 2 months of dapsone therapy. Reversible hepatic injury has been reported with dapsone and can be either hepatocellular or cholestatic.[91, 92]

Dapsone-induced hepatotoxicity usually is considered a hypersensitivity reaction (referred to as sulfone syndrome); symptoms include fever, malaise, jaundice, exfoliative dermatitis, lymphadenopathy, methemoglobinemia, and hemolytic anemia. This syndrome is rare, and hepatic involvement ranges from mild increases in transaminase levels to fatal fulminant hepatitis.[91] Dapsone-induced hepatitis without the classic features of sulfone syndrome also has been described.[92]

Trimetrexate, an antimetabolite, is a potent inhibitor of the *P. jiroveci* dihydrofolate reductase.[93] Addition of leucovorin protects mammalian cells from the cytotoxic effects of the drug without affecting the anti–*P. jiroveci* effect. Despite its potent enzymatic inhibition, trimetrexate is less effective than TMP-SMX or pentamidine in treating severe *P. jiroveci*.[93] It is administered infrequently to patients with moderate-to-severe hypoxia who cannot tolerate initial treatment with TMP-SMX or pentamidine or for whom treatment failed. Abnormal liver transaminase levels have been reported in 6–15% of patients treated with trimetrexate-leucovorin.[94, 95]

Atovaquone, an alternative agent for prophylaxis and treatment of mild-to-moderate *P. jiroveci*, does not appear to cause hepatotoxicity.

Antiherpes and Anticytomegalovirus Agents

Acyclovir is a synthetic purine nucleoside analog with in vitro and in vivo inhibitory activity against herpes viruses (herpes simplex and varicella zoster). It is well tolerated even during long-term administration; its most common side effects are nausea, diarrhea, headache, and malaise. Rare cases of elevated transaminase levels, clinical hepatitis, and jaundice have been reported.[96, 97] Valacyclovir, a valine-esterified form of acyclovir with an extended half-life, is rapidly converted to acyclovir in vivo, and during clinical trials, elevations in transaminase levels were no more frequent than with placebo, according to the

label information. Rare cases of hepatitis due to this agent have been observed during clinical practice.[98] Famciclovir, the oral prodrug of penciclovir, has caused only mild elevations of transaminase and bilirubin levels in less than 3% of patients, according to the label information.

Ganciclovir, an acyclic synthetic guanine derivative related to acyclovir, is used primarily for the treatment of cytomegalovirus disease and may cause mild abnormalities in liver function.[99–101] Significant hepatotoxicity has been reported only rarely in patients with HIV being treated for cytomegalovirus retinitis with ganciclovir.[102, 103] The onset of ganciclovir hepatotoxicity occurs within the first 2 weeks of treatment and tends to resolve within 2 weeks after withdrawal of the agent.[102, 103] Whether this is a dose-related phenomenon and what the mechanism is that causes the hepatotoxicity are both unknown.

The most recent addition to this drug class is valganciclovir, another valine-esterified compound, which is rapidly converted to ganciclovir and has equivalent bioavailability to the parenteral formulation of ganciclovir. Thus far, no serious hepatotoxicity has been reported with this agent.

Foscarnet, a pyrophosphate analog available only intravenously, is another agent active against herpes viruses. Liver toxicity has been reported rarely in patients without HIV treated with this agent.[104]

Lipid-Lowering Agents

Hyperlipidemia has become a significant comorbid problem for patients with HIV. The risk of developing lipid abnormalities increases with duration of HIV treatment and exceeds 50% of patients after 2 years.[105] Though most commonly associated with HAART, specific agents as well as HIV may contribute to these abnormalities. Most clinicians believe it is appropriate to manage these disorders according to current guidelines from the AIDS Clinical Trials Group.[106] Although optimal treatment strategies for hyperlipidemia associated with HIV remain undefined, many patients receiving HAART are taking one or more lipid-lowering agents.

Among the most widely prescribed agents for lowering total and low-density lipoprotein cholesterol are the analogs of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins). These are prodrugs, which competitively inhibit the HMG-CoA reductase enzyme. Clinical trials in patients without HIV have shown that statins are well tolerated and are associated with a low rate of treatment withdrawal due to adverse effects.[107] Hepatotoxicity during therapy with statins is rare and is manifested primarily as asymptomatic transaminase elevations in 1–2% of patients. These elevations are transient and often dose related, and usually revert to normal while therapy is continued. Hepatocellular injury usually reverses with discontinuation. Cases of documented liver failure due to statins are rare.[108]

The lack of large-scale studies on the safety of statins in patients with HIV warrants close monitoring of these patients during treatment. Predisposing factors for hepatotoxicity, such as chronic liver disease (e.g., hepatitis C virus) and polypharmacy, are more common among these patients. Drug-drug interactions may play a significant role. In patients with HIV, inhibition of CYP3A4 by commonly prescribed drugs (e.g., clarithromycin, azoles, and protease inhibitors) can increase serum levels of all statins (except pravastatin) several-fold. In a small study of patients with HIV and hyperlipidemia who were treated with statins (most received lovastatin and simvastatin), transaminase elevations occurred in approximately 7%, a much higher number than reported in similar studies with HIV-negative patients.[109] Larger studies are needed to confirm this observation.

Anabolic Steroids

Another frequent manifestation of prolonged survival with HIV is the wasting syndrome. Anabolic steroids (e.g., nandrolone, oxandrolone, and oxymetholone) are synthetic analogs of testosterone that have been administered for HIV-associated wasting. In both men and women with HIV, they are well tolerated but may be associated with serious hepatotoxicity.[110–112] Transaminase elevations may occur in 10–20% of patients receiving anabolic steroids.[110–112] Cholestatic jaundice, occurring within 1–10 months after onset of treatment, is the major hepatic side effect of this drug class and is dependent on both the dosage and duration of therapy. Prolonged administration of high dosages of anabolic steroids has been associated with peliosis hepatis, an otherwise uncommon vascular lesion of the liver, and may result in liver failure and neoplasms.[112, 113] Benign and malignant hepatic tumor formation also has been

associated with anabolic steroids, and tumor regression has been reported after cessation of treatment.[114, 115]

In an analysis of the hepatotoxicity of oxymetholone in 30 patients with advanced HIV disease, the most common laboratory abnormalities were mild elevations in γ-glutamyl transferase in 17% of treated patients and significant elevations of total bilirubin in 10%.[116] One patient in this study developed a liver lesion consistent with peliosis hepatis.

Conclusion

Hepatotoxicity is reported increasingly in patients with HIV. The most recent focus has been the toxicity of the nucleoside and nonnucleoside reverse transcriptase inhibitors and HIV-1 protease inhibitors. However, the etiology for elevated transaminase levels in these patients is often multifactorial, confounded by chronic hepatitis B or C, alcohol consumption, concurrent drugs and herbal therapies, and a multitude of drug-drug interactions. The challenge for clinicians is to recognize the potential contributors and drug interactions, and thus prevent serious adverse consequences. The challenge for investigators is to define drug-induced hepatotoxicity prospectively using clear biochemical, pharmacologic, and histologic markers, to elucidate the mechanisms of hepatic injury, to determine the specific causative agents, and to control for multiple confounding biases. With this further understanding, we then can proceed to determine whether preventive measures may help reduce the risk.

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