Abacavir Hypersensitivity Reaction

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A hypersensitivity reaction occurs in association with initiation of abacavir therapy as part of combination antiretroviral therapy in ∼3.7% of patients. The reaction is possibly the result of a combination of altered drug metabolism and immune dysfunction, which is poorly understood. White patients appear to be at higher risk and patients of African descent at lower risk of abacavir hypersensitivity. Clinical management involves supportive measures and discontinuation of abacavir therapy. Rechallenge with abacavir in a hypersensitive patient should be avoided because it might precipitate a life-threatening reaction.

Adverse drug reactions occur frequently in patients with highly active antiretroviral therapy (HAART) [1]. Abacavir is a relatively new antiretroviral agent and is used in many HAART regimens. Abacavir is available in a single-drug tablet and a combination tablet (with zidovudine and lamivudine). Abacavir is associated with a hypersensitivity reaction, a systemic illness that can be fatal if abacavir use is continued despite the reaction or if rechallenge occurs in someone who has already experienced the reaction. Clinicians who prescribe abacavir must be knowledgeable about this hypersensitivity reaction, during both diagnosis and clinical management, so that the safety of patients can be maintained while they benefit from its antiretroviral efficacy.

ABACAVIR

Abacavir is a nucleoside analogue reverse-transcriptase inhibitor of HIV type 1 (HIV-1) replication. Abacavir is a deoxy-guanosine base and is metabolized into carbovir triphosphate, the active intracellular agent. Abacavir has similar in vitro potency to other nucleoside analogues [2, 3].

Abacavir has an oral bioavailability of 83% and CNS area under the curve (AUC_{CNS}) to plasma AUC_{0–6} ratios with a range of 27%–33% [4, 5]. The current recommended dose is 300 mg administered orally twice per day in combination with other antiretroviral agents. Abacavir is metabolized by the liver, but it does not inhibit or induce cytochrome P-450 enzymes and does not interact with medications metabolized by this system [6].

In clinical trials involving children and adults naive to antiretroviral therapy, abacavir in combination with zidovudine and lamivudine has resulted in an average reduction of ∼2 log_{10} in plasma HIV RNA level [7–16]. Use of abacavir in combination with ≥3 antiretrovirals can be part of a successful salvage therapy as well [16–18].

DRUG-RELATED HYPERSENSITIVITY

Hypersensitivity to medication is a life-threatening reaction that results in a systemic illness that usually includes fever and maculopapular rash accompanied by constitutional symptoms (fatigue, malaise, myalgias, and arthralgias), multivisceral involvement (lymphadenopathy, mucositis, pneumonitis, myocarditis, hepatitis, and interstitial nephritis), and hematologic abnormalities (atypical lymphocytosis and eosinophilia) [19]. Hypersensitivity is also known as DRESS (drug
rash with eosinophilia and systemic symptoms) syndrome.

Hypersensitivity can be induced by aromatic anticonvulsants (including phenytoin, carbamazepine, and lamotrigine) [20], sulfonamides (including sulfamethoxazole and dapsone) [21], β-lactam antibiotics (including penicillins and cephalosporins) [22], antineoplastic agents (including 1-asparaginase and paclitaxel) [23], and antirheumatic drugs (including allopurinol, diclofenac, and fenoprofen) [24]. Antiretroviral agents reported to induce hypersensitivity reactions include zidovudine [25], didanosine [26], zalcitabine [27], delavirdine [28], nevirapine [29], efavirenz [30], and amprenavir [31].

Trimethoprim-sulfamethoxazole causes rash and fever in up to 50% of HIV-positive patients. The rash can be treatment-limiting or severe in up to 20% of HIV-positive patients who receive it. Adverse reactions, such as nausea, also occur. However, severe hypersensitivity involving systemic manifestations, such as hypotension and pulmonary infiltrates, have been noted in 8 case reports of HIV-positive patients who had a previous adverse reaction and who were rechallenged with trimethoprim-sulfamethoxazole, according to a review of the literature from 1994–1999 [32].

**EPIDEMIOLOGY**

Abacavir hypersensitivity has been reported in both children and adults. The incidence in clinical trials has a range of 0%–14% [7–18, 32]. Overall, the incidence appears to be ~3.7%, or 1 case among every 25 patients who receive the drug [33]. Retrospective studies from both clinical trials and routine patient care have attempted to determine risk factors for the development of abacavir hypersensitivity. In an analysis of 5332 patients enrolled in abacavir clinical trials, being antiretroviral therapy–experienced at the start of abacavir therapy and being of African descent were associated with a nearly 40% reduction in the risk of hypersensitivity [34]. In a study of 540 patients that included a predominance of ethnic and racial minorities, Hispanic ethnicity was associated with an OR of 2.77 when compared with other ethnic backgrounds [32]. Patients of white race were found to be at significantly greater risk in another study of a population with a low percentage of ethnic minorities [35].

There have been reports that abacavir hypersensitivity has occurred in patients who interrupt receipt of abacavir therapy without having had hypersensitivity and who subsequently restart therapy, but this is believed to be rare [36]. A study of 145 patients who interrupted abacavir treatment showed 1 case of hypersensitivity but no statistical difference in incidence between the study patients who did not interrupt abacavir [37].

**PATHOGENESIS**

Altered or unusual drug metabolism and a susceptible immune system are believed to be important cofactors for the development of drug-related hypersensitivity [38]. In certain individuals, a chemically reactive metabolite is formed that is unable to be or is inadequately detoxified, leading to immune activation and, ultimately, cellular damage [39]. There are at least 2 possible reasons for the systemic nature of the reaction: (1) the chemically reactive metabolite arises in the liver and is transported to other tissues, where the immune-mediated damage occurs; or (2) the metabolite arises from organ-based metabolism outside the liver. Certain cell types present in lung, skin, and bone marrow have ample stores of cytochrome P-450, it is extremely difficult to predict these idiosyncratic hypersensitivity reactions [43].

HIV-infected persons are likely to be at special risk of developing hypersensitivity reactions because of the disease-associated perturbations in the immune system [44, 45]. Abacavir hypersensitivity, as well as that seen with nevirapine and efavirenz, resembles a delayed hypersensitivity reaction that is different from the immediate hypersensitivity, anaphylactic-type reaction seen with penicillin. The Th2 response that predominates in HIV-infected persons [46] also promotes delayed hypersensitivity [47]. For example, with nevirapine therapy, greater rates of hepatotoxicity, which is a form of hypersensitivity, occur at higher CD4 cell counts [48]. In addition, cytokines, such as IL-1β, IL-6, and TNF-α, are known to influence the cytochrome P-450 system, altering drug metabolism [49]. This may be the case for sulfamethoxazole and may explain its high rate of hypersensitivity reactions in HIV-positive patients [50].

The exact metabolite that is likely to be responsible for hypersensitivity is unknown. Two pathways primarily metabolize abacavir. Oxidation occurs via alcohol dehydrogenase, and glucuronidation occurs via uridine diphosphate glucuronyl transferase [3]. Neither of the resulting metabolites has antiviral activity. It is likely that other minor pathways, which are present in only a small percentage of the population, result in a chemically reactive metabolite. Such metabolites and potential metabolite-protein complexes are difficult to detect.

Abacavir hypersensitivity has been observed in patients with
a wide range of CD4 cell counts [7–18]. In multivariate analyses of retrospective cohorts, CD4 cell count does not appear to be significantly related to abacavir hypersensitivity [34, 35]. HIV-positive children aged >3 months display hypersensitivity reactions identical to those of adults [10], which suggests that a minimally active or controlled immune system is all that is needed for hypersensitivity to abacavir to occur.

Preliminary studies appear to confirm the role of the immune system in abacavir hypersensitivity. Patients who were hypersensitive were found to produce more IL-4 than were HIV-positive patients who were not hypersensitive. There was also a decrease in Th1 cells with an increase in the number and distribution of Th0, Th2, Tc0, and Tc2 cells [51]. In one study, skin samples obtained from patients with abacavir hypersensitivity were examined. A lack of lymphocyte involvement in the epidermis distinguished the rash from Stevens-Johnson syndrome. CD8 cells predominate along with high numbers of CD4 cells [52].

**CLINICAL SPECTRUM**

The most common symptoms of abacavir hypersensitivity are fever, rash, nausea, vomiting, diarrhea or abdominal pain, and fatigue and malaise [53]. Occasionally, respiratory symptoms, such as tachypnea, cough, and pharyngitis, are prominent, and the reaction can therefore mimic pneumonia. Thus, the diagnosis of abacavir hypersensitivity may be overlooked; abacavir therapy may thus be continued and symptoms may worsen, possibly resulting in death.

Gastrointestinal symptoms are usually the most prominent, after fever and rash. At one center, 15 HIV-positive patients who had symptoms of abacavir hypersensitivity were compared with 30 HIV-positive patients who had symptoms of influenza [54]. Gastrointestinal symptoms occurred in 60% of patients with abacavir hypersensitivity versus 6% of patients with influenza. Although fever and myalgia were commonly observed in both groups, rash occurred in 47% of the patients with hypersensitivity and in only 6% of patients with influenza. Although demographic characteristics, vital signs, and laboratory tests did not differ between the groups, respiratory symptoms that occurred without gastrointestinal symptoms were much more likely to be caused by influenza than by abacavir hypersensitivity. Although cutaneous involvement is a prominent part of nevirapine and efavirenz hypersensitivity, the rash caused by abacavir hypersensitivity may often be clinically unimpressive. Rash only occurs in 70% of cases [33]. Fever may often occur before the rash appears. Pruritus is also not prominent, and toxic epidermal necrolysis has not been reported. Sometimes the patient is unaware that the rash is present. In children, there may be difficulty in distinguishing abacavir hypersensitivity reaction from common viral exanthems. Abnormal laboratory findings may occur, but they are no means specific or diagnostic [33]. Eosinophilia is not usually present. Leukopenia, anemia, and thrombocytopenia may all occur. There may be elevations in transaminase levels, as well as in alkaline phosphatase, blood urea nitrogen, serum creatinine, and lactic dehydrogenase levels.

More than 93% of abacavir hypersensitivity reactions occur during the first 6 weeks of treatment [53]. The median time to develop the reaction is 8 days. The reaction can develop on the first day of receipt of abacavir therapy and has been reported to occur up to 160 days after initiation. Patients may actually report experiencing symptoms within hours of receipt of each dose. It is characteristic of abacavir hypersensitivity that, once the reaction has become clinically apparent, the severity of the reaction tends to worsen with receipt of each successive dose.

Symptoms appear suddenly and worsen over just a few days, when use of abacavir is continued. Many patients require hospitalization, especially when abacavir hypersensitivity is not in the differential diagnosis of the treating physician. Symptoms of hypersensitivity tend to improve in 2 days and may resolve completely just a few days later. However, in some patients, symptoms may continue to worsen for several days, even after abacavir is discontinued before clinical improvement occurs. If use of abacavir is discontinued in time to prevent the development of hypotension, the hypersensitivity reaction is completely reversible.

Early in the development of abacavir, patients who were rechallenged the drug experienced unanticipated life-threatening consequences. Among 112 patients with abacavir hypersensitivity who were rechallenged, an anaphylactic or immediate type of hypersensitivity reaction occurred in 20% [55]. Hypotension, renal insufficiency, and bronchoconstriction have resulted in death. Rechallenge symptoms are usually seen with the administration of the first dose or doses during the rechallenge period. Therefore, patients with clinically suspected abacavir hypersensitivity should not be rechallenged.

A fever that develops within a few weeks after the initiation of therapy with abacavir may be due to causes other than hypersensitivity. Most common is the likelihood that simultaneous initiation of treatment with drugs, such as trimethoprim-sulfamethoxazole, efavirenz, or nevirapine, may be the cause. The incidence of hypersensitivity to each of these drugs is greater than that of abacavir [29, 30, 56]. The presence of gastrointestinal or respiratory symptoms that accompany a rash or fever should lead to greater consideration of abacavir hypersensitivity as the likely cause. Opportunistic infections can manifest shortly after initiation of HAART as a result of immune reconstitution and should also be considered.

The decision whether to stop abacavir therapy or to cautiously continue it is an important one. On the one hand,
Abacavir may be an important component of an antiretroviral regimen that the clinician and the patient would prefer not to stop unless absolutely necessary, perhaps because other alternatives are lacking. On the other hand, the potential severity of abacavir hypersensitivity calls for prudence. It is clear that abacavir use should be discontinued if the timing, severity, and combination of symptoms are suggestive. If it is not clear, the doctor may wish to consider asking the patient to take an additional dose and report back within a few hours to see if the symptoms worsen. If symptoms do worsen, abacavir use should be discontinued. If symptoms do not worsen, abacavir use may be cautiously continued while other possible causes of the patient’s symptoms are investigated.

**CLINICAL MANAGEMENT**

The key to appropriate clinical management is early and accurate recognition of abacavir hypersensitivity. Clinical suspicion should be high if the symptoms appear within the first 6 weeks of abacavir therapy, if the symptoms appear together as both constitutional and organ specific (particularly gastrointestinal symptoms), and if the symptoms worsen with each successive dose.

Physicians who are inexperienced in the care of HIV-positive patients are less likely to recognize or be aware of abacavir hypersensitivity and may mistakenly advise patients to rechallenge when symptoms resolve. Thus, doctors who care for HIV-positive patients, whether in an ambulatory care, long-term care, or emergency department setting, should be watchful for hypersensitivity when evaluating someone who has recently initiated abacavir therapy. Therapy is totally supportive: intravenous hydration and withdrawal of abacavir (as well as all other antiretroviral agents being administered at that time) are its cornerstones. Antipruritics and corticosteroids do not generally provide much relief. Antiemetics and analgesics may be needed for a short period of time.

A discussion of the potential for hypersensitivity is warranted when prescribing abacavir. In the United States, a patient information card is distributed with each bottle of the drug. If not informed about this “warning” card, patients may become frightened when they read it and may not initiate abacavir therapy while initiating treatment with their other medications, resulting in suboptimal antiretroviral therapy. Patient should be educated about the nature and timing of symptoms of potential abacavir hypersensitivity. The message to stop antiretroviral therapy when instructed to do so is in opposition to the adherence education now routinely provided, which stresses the importance of not stopping antiretroviral therapy or missing doses. Thus, enthusiastic patients may unknowingly contribute to the severity of the reaction by continuing abacavir therapy without discussing the symptoms with their health care providers.

To ensure the safe and successful administration of abacavir, clear communication is essential. Patients should know who to call, how to call, what to look for, and where to seek medical attention, should they be unable to reach their health care provider. One group has delineated procedures prescribing and responding to patients with potential abacavir hypersensitivity [57]. An important feature is informing the on-call physician about which patients have recently initiated abacavir therapy and who, therefore, are at risk.

There are no established interventions that will preempt the development of abacavir hypersensitivity. Patients randomized to receive prednisone for the first 2 weeks when initiating abacavir therapy in combination with nevirapine (along with zidovudine and lamivudine) experienced the same prevalence of hypersensitivity (although it could have been due to the nevirapine) as patients who did not receive prednisone [58].

**SUMMARY**

Abacavir hypersensitivity is a reversible, immune-mediated, systemic reaction that generally occurs within the first 6 weeks of treatment. When abacavir use is discontinued, the symptoms resolve during the course of a few days. Early recognition, discontinuation of abacavir use, and administration of supportive therapy aimed at symptomatic relief are the keys to clinical management. Appropriate patient education, along with a clear plan for communication in the event of suspected symptoms, is critical to the safe administration of abacavir. Efforts to identify which patients are at risk, and to whom administration of abacavir should be avoided, are needed.

**References**


