Educational Material for healthcare professionals

Abacavir is an inhibitor of the reverse transcriptase of the HIV virus and indicated for antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults.

Hypersensitivity reaction (HSR) is the major points of concern with abacavir. These potentially serious reactions are characterized by the appearance of symptoms indicating multi-organ system involvement. Nearly all patients with HSR experience fever or rash.

Major symptoms associated with abacavir hypersensitivity:

- Fever (~80%)
- Presence of skin rash (~70%)
- Gastrointestinal symptoms (>50%) such as nausea, abdominal pain, vomiting, and diarrhoea
- Generalize malaise, fatigue, and headache (~50%)
- Other symptoms (~30%) such as respiratory symptoms (includes dyspnoea, pharyngitis or cough in the initial presentation), mucosal, and musculoskeletal symptoms.

Patients SHOULD CALL THEIR DOCTOR IMMEDIATELY for advice on whether they should stop taking abacavir If:

• Presence of skin rash; OR

• Development of 1 or more symptom from at least 2 of the following groups:

Fever

Shortness of breath, sore throat or cough

Nausea or vomiting or diarrhoea or abdominal pain

Extreme tiredness or achiness or generally ill feeling

The **risk factor HLA-B*5701** is the only identified pharmacogenetic marker that is consistently associated with clinical diagnosis of hypersensitivity reactions. However, some patients with a suspected hypersensitivity reaction may not have the HLA-B*5701 allele.

It is recommended that before initiating abacavir therapy, clinicians should screen for HLA-B*5701(in settings where validated screening methods are available). Clinical diagnosis of suspected hypersensitivity to remains the basis for clinical decision making. HLA-B*5701 screening for risk of hypersensitivity should never be substituted for appropriate clinical vigilance and patient management in individuals receiving abacavir. If hypersensitivity cannot be ruled out on clinical grounds, abacavir should be permanently discontinued and should not be restarted, regardless of the results of HLAB*5701screening. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.

The one-time HLA-B*5701 test identifies people at high risk for this serious allergic reaction. The gold standards for HLA-B*5701 screening are sequence-based genotyping and polymerase chain reaction sequencing of specific oligonucleotide probes. Blood or saliva samples are collected and tested for genetic sequences coding for the HLA-B*5701 allele. Results of PREDICT-1 and SHAPE studies show that the presence of the HLA-B*5701 allele is associated with increased risk of abacavir hypersensitivity, regardless of race, screening for HLA-B*5701 before starting treatment with abacavir may identify subjects at increased risk of a hypersensitivity, avoiding treatment with abacavir in subjects with the HLA-B*5701 allele was shown to significantly reduce the incidence rate of clinically diagnosed cases of hypersensitivity. Data from these studies do not support the use of skin patch testing in routine clinical practice. Only patients found to lack the HLA-B*5701 allele should begin therapy with abacavir.

Management of abacavir hypersensitivity reaction:

Symptoms can occur at any time during treatment with abacavir, but usually occur within the first 6weeks of therapy. Symptoms are initially mild and evolve over days, becoming more severe with continued abacavir therapy. Symptoms improve on cessation of abacavir. Re-challenge (re-introduction) can result in a more rapid and severe reaction, which can be fatal, therefore re-challenge (re-introduction) is contraindicated

Some patients with hypersensitivity reactions were initially thought to have gastroenteritis, respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. A delay in diagnosis of hypersensitivity can result in abacavir being continued or re-introduced, leading to more severe hypersensitivity reactions or to death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these disease.

The educational material includes case studies to demonstrate different clinical scenarios and their management.

Case studies for hypersensitivity reaction

Case #1

- A 46-year-old woman, newly diagnosed with HIV infection, initiated therapy with abacavir, lamivudine and efavirenz.
    - HLA-B*5701 status is unknown.
- On day 8 of therapy, her physician noted a mild pruritic rash on her neck and trunk.
    - The patient was afebrile, had no gastrointestinal symptoms, and felt well
    - She did not have any muscle or joint aches, respiratory symptoms, or tenderness or swelling of the lymph nodes
    - She had not taken any other medications

- Differential diagnoses include:
    - A reaction to efavirenz
    - Abacavir hypersensitivity
    - Immune reconstitution syndrome.
- Course of action:
    - Patient has a single mild symptom, so monitor closely for possible resolution or progression of symptoms before making a decision:
        - Review symptoms of hypersensitivity
        - Instruct the patient to continue all medications and immediately contact physician, if other symptoms develop
        - Re-evaluate the patient after 24 hours

- Follow-up:
    - Patient continued all medications
    - Rash improved over the next 4 days with no further symptoms
- Conclusion:
    - Patient had a transient efavirenz-related rash (and not a hypersensitivity reaction)

Case #1 – alternative scenario

- After noticing the rash for 3 days, the patient discontinued all medications; the rash has since disappeared.
- Course of action:
    - Permanently discontinue abacavir: Although the reaction may have been an efavirenz rash, by stopping all drugs, it is no longer possible to differentially diagnose an abacavir hypersensitivity reaction without exposing the patient to the risk of reintroduction**.**

Case #1 summary

- A single symptom is not sufficient for a diagnosis of hypersensitivity reaction
    - **Drug interruption after a single symptom should be avoided**
        - Resolution of symptom off-drug makes a differential diagnosis impossible
    - However, **if abacavir is interrupted, it should not be restarted**
        - Resolution of symptom may represent aborted evolution of a multi-symptomatic hypersensitivity reaction
        - Reintroduction of the drug puts the patient at risk for a reaction during reintroduction
        - Left-over Abacavir tablets should be retrieved from patient to avoid the risk of reintroduction
- Take a careful history, and review for other symptoms
- Continue to closely monitor the patient

- Avoid corticosteroids, which could mask the development of additional symptoms
- Use antihistamines, if necessary

Case #2

- A 29-year-old male with a history of (herpes simplex virus) HSV and syphilis
- Newly diagnosed with HIV, low CD4 (<200 cells/mm^3), and high viral load.
- Negative screening result for HLA-B*5701
- Initiated medications with abacavir, lamivudine and lopinavir/r
- Concomitant medications:
    - Valacyclovir (chronic medication) initiated before antiretroviral therapy
    - Co-trimoxazole initiated with antiretroviral
- **Day 8**: Patient noted myalgias and low-grade fever peaking at 37.8°C.
- **Day 9**: Patient noted faint rash with low-grade fever peaking at 39°C approximately 9 hours after morning dose.
- **Day 10**: Patient experienced same symptoms at the same time after morning dose, but fever peaked at 38°C with fewer myalgias.
- **Day 11**: Patient was evaluated in clinic:
    - Temperature 37°C
    - Generalized fine urticarial rash
    - Asymptomatic
- Course of action:
    - Symptoms appear to be resolving each day despite continued administration of abacavir over several days
    - Symptom resolution and the patient's negative HLA-B*5701 screening status suggest another aetiology
    - Continue administration of abacavir with close monitoring and discontinue co-trimoxazole
- Follow-up:

  - Co-trimoxazole is stopped on day 11; patient is seen in the clinic on days 12 and 13, and symptoms continue to decline in severity
  - Patient is given topical steroids and antihistamines for the rash
  - By day 15, rash and myalgias have resolved and patient remains afebrile on abacavir, lamivudine, and lopinavir/r

- Conclusion:
  - Co-trimoxazole allergy

Case #2 – alternative scenario

- Patient is seen on days 12 and 13; symptoms continue, but do not increase or decrease in severity.
- Patient is given topical steroids and antihistamines for the rash.
- By day 15, rash is resolving but myalgias continue; patient complains of malaise.
- Course of action:
  - Permanently discontinue abacavir, if no other cause of the patient's symptoms is identified; in this case, abacavir hypersensitivity cannot be definitively ruled out.
- Consider other causes for rash and fever when patient is taking concurrent medications known to be associated with these symptoms or allergies, particularly, if screening suggests a low risk of abacavir hypersensitivity reaction
- However, a negative HLA-B*5701 screen does **not** definitively rule out the possibility of a hypersensitivity reaction
  - If a diagnosis of abacavir hypersensitivity cannot be excluded, then abacavir must be permanently discontinued, regardless of the results of any test

Case #3

- 45-year-old male initiated medication with abacavir, lamivudine and boosted fosamprenavir.
  - HLA-B*5701 status unknown.
- **Day 5**: Onset of vomiting.
- **Day 6**: Onset of diarrhea; nausea worsens with more frequent vomiting.

- **Day 7**: Development of fever to 39°C and general weakness; gastrointestinal symptoms continue without further increase in severity; careful examination revealed no rash.

- Course of action:

    - Permanently discontinue abacavir

        - Cumulative, multi-organ symptomatic onset indicates a high probability of a developing abacavir hypersensitivity reaction

- Follow-up:

    - Within 24 hours of abacavir discontinuation, patient is afebrile and gastrointestinal symptoms are resolving

- Conclusion:

    - Patient experienced abacavir hypersensitivity reaction

Case #3 summary

- Rash is very common in abacavir hypersensitivity; however, just as rash alone would not be sufficient for a diagnosis of a hypersensitivity reaction, neither the absence of rash is a reason to exclude a diagnosis of hypersensitivity in the presence of other compatible symptoms; rash may occur late or even after discontinuation of abacavir

- Other features point towards the diagnosis of a hypersensitivity syndrome

- Patient developed multi-organ involvement, including constitutional and gastrointestinal symptoms

    - Even in the absence of a rash, patient's symptoms point to a possible diagnosis of abacavir hypersensitivity reaction

- Symptoms did not appear all at once, but in a gradual manner

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions to Mylan on +44 (0) 800 1218267 or UKPharmacovigilance@mylan.com

You can also report side effects directly via the national reporting system:
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin Tel: +353 1 6764971
Fax: +353 1 6762517 Website: www.hpra.ie email: medsafety@hpra.ie