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ACPE Universal Program Number
407-000-07-010-H01
1 credit hour (0.1 CEU) Expires: 3/31/10

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RETISERT

Goal

To present the epidemiology, etiology, diagnosis, and current treatment options available for uveitis; discuss the advantages and disadvantages of the various routes of steroid administration; review Retisert; and provide the rationale for drug treatment of uveitis.

Objective

After reviewing this article, the reader should be able to:

1. define the epidemiology and etiology of uveitis;
2. identify the ocular manifestations and potential consequences of untreated uveitis;
3. compare and contrast the different routes of corticosteroid use for the treatment of uveitis;
4. describe the advantages and disadvantages of Retisert as a treatment option for uveitis;
5. recognize the limitations of Retisert based on the published data available to date and the economic implications.

Test Questions

1. Which choice *best* describes attributes of uveitis?

- (a) an intraocular inflammatory condition that never has bilateral involvement
- (b) a condition that primarily occurs in the elderly

- (c) inflammation that involves the ciliary body, retina, iris, and choroid
- (d) an ocular condition that can be caused by infection, autoimmune disease, or trauma

2. A 45-year-old woman presents to a clinic with blurred vision, ocular pain, sensitivity to light, tearing, and redness. She does not report the presence of floaters. What type of uveitis could this be?

- (a) posterior
- (b) anterior
- (c) intermediate
- (d) nongranulomatous

Questions 3–8 refer to the following case:

A 38-year-old male is newly diagnosed with posterior uveitis.

3. What would you counsel him about the prognosis of the disease?

- (a) If left untreated, the disease will gradually subside, with no long-term consequences.
- (b) If left untreated, chronic inflammation can lead to structural damage and vision loss.
- (c) If left untreated, chronic inflammation can lead to structural damage, but vision remains intact.
- (d) If left untreated, acute inflammation can lead to permanent vision loss.

4. The physician decides that the patient requires treatment. What is the current mainstay for initial treatment of uveitis?

- (a) nonsteroidal antiinflammatory drugs (NSAIDs)
- (b) immunosuppressants

- (c) antibiotics
- (d) corticosteroids

5. The patient did not achieve adequate inflammatory control of the uveitis with topical therapy. The next treatment that he received was periocular injections. How often will he need to return for repeat injections?

- (a) weekly
- (b) every 4–6 weeks
- (c) every 4–6 months
- (d) yearly

6. Six months later, the patient's disease remains uncontrolled. In addition, the uveitis is now bilateral. At this time, oral prednisone therapy is started. Which of the following adverse effects may occur?

- (a) increased susceptibility to infections
- (b) hypoglycemia
- (c) drowsiness
- (d) hypotension

7. After 4 months of oral prednisone therapy, the patient has developed adverse effects such as weight gain and psychosis. What should be done to minimize these adverse effects?

- (a) Switch the systemic corticosteroid to a topical ocular steroid with no tapering needed.
- (b) Taper the systemic steroids and consider other routes of corticosteroid administration (eg, periocular, intravitreal, implant placement).
- (c) Stop the systemic corticosteroid (no tapering needed) and start immunosuppressive therapy.
- (d) Continue the systemic corticosteroid and add NSAIDs.

8. The patient's physician decides to use Retisert implants as the next treatment option. Retisert is approved for the treatment of:

- (a) anterior uveitis.
- (b) acute angle-closure glaucoma.
- (c) chronic, noninfectious, posterior uveitis.
- (d) cystoid macular edema.

9. Which of the following statements concerning corticosteroid intravitreal implants is *true*?

- (a) They reduce the risks of ocular toxicity secondary to steroids.
- (b) Biodegradable materials are used in implants for chronic disease.
- (c) They were developed because corticosteroids are the mainstay of therapy for uveitis and conventional routes of administration are often inadequate.
- (d) The first drug studied as a corticosteroid implant was fluocinolone acetonide.

10. According to trials done in humans, Retisert reaches a steady-state concentration lasting approximately how long?

- (a) 6 months
- (b) 12 months
- (c) 30 months
- (d) 5 years

11. In the Phase III clinical trials evaluating the efficacy of Retisert:

- (a) patients were diagnosed with acute and chronic uveitis.
- (b) the more severely affected eye was evaluated when bilateral disease was present.
- (c) the primary outcome was improvement in visual acuity.
- (d) no differentiation was made between patients with anterior versus posterior disease.

12. Positive results observed with Retisert therapy in clinical trials include:

- (a) reduction of intraocular pressure.
- (b) no difference in recurrence rate versus placebo.
- (c) reduction in adjunctive therapy.
- (d) no change in visual acuity.

13. According to the clinical trials in humans, which of the following adverse effects was most commonly seen with Retisert therapy that may potentially require intervention?

- (a) reduction in visual acuity requiring prescription glasses
- (b) increase in intraocular pressure requiring treatment
- (c) recurrence of disease requiring the addition of NSAIDs
- (d) infection requiring antibiotics

14. Due to the lack of data on the long-term effects of Retisert, the FDA has required that a postmarketing analysis be conducted. Which of the following is a potential complication of Retisert therapy that will be specifically evaluated?

- (a) recurrence rate
- (b) number of patients requiring adjunctive therapy
- (c) number of cataract extractions
- (d) number of infections

15. Which of the following statements based on the currently available data for Retisert is true?

- (a) Efficacy beyond one year of therapy is not known.
- (b) Therapy has been shown to improve patients' quality of life.
- (c) Despite its high cost, the cost benefit has been clearly established.
- (d) The safety of use in both eyes simultaneously is not known.

ACPE Universal Program Number
407-000-07-011-H01
1 credit hour (0.1 CEU) Expires: 3/31/10

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ALISKIREN FOR RENIN INHIBITION

Goal

To present the safety, efficacy, pharmacology, pharmacokinetics, and drug interactions of aliskiren.

Objectives

After reviewing this article, the reader should be able to:

1. describe the unique mechanism of action of aliskiren;

2. distinguish the pharmacology of renin inhibition from ACE inhibitors and ARBs;
3. assess the clinical role of aliskiren in patients with mild to moderate hypertension;
4. select an appropriate dosing regimen for a patient beginning aliskiren therapy;
5. assess the potential for aliskiren combination therapy with other antihypertensives.

Test Questions

1. What percentage of hypertensive patients in the US achieve blood pressure goals?

- (a) 21%
- (b) 34%
- (c) 46%
- (d) 59%

2. Which of the following is not an end-organ effect of angiotensin II?

- (a) vasoconstriction
- (b) myocardial hypertrophy
- (c) thrombogenesis
- (d) tachycardia

3. Which of the following is not a stimulus for increased renin secretion?

- (a) reduced sympathetic tone
- (b) reduced renal perfusion pressure
- (c) reduced plasma volume
- (d) reduced angiotensin II concentration

4. Which of the following statements concerning aliskiren pharmacokinetics is true?

- (a) Aliskiren should not be taken within 1–2 hours following meals high in divalent cations (calcium, magnesium).
- (b) Aliskiren is highly protein bound.
- (c) Aliskiren should be dose adjusted for patients with creatinine clearance of 30–60 mL/min
- (d) Aliskiren is primarily eliminated unchanged in the feces.

5. Which of the following therapy combinations would be expected to produce an increase in angiotensin II concentration?

- (a) valsartan plus aliskiren
- (b) losartan plus amlodipine
- (c) lisinopril plus amlodipine
- (d) aliskiren plus hydrochlorothiazide

6. A 58-year-old male presents to the clinic for follow-up one month after starting enalapril 10 mg twice daily for newly diagnosed hypertension. He reports complete adherence to his new medication, but complains of a dry cough throughout most of the day that has troubled him since starting enalapril. His primary care provider wishes to start an antihypertensive that will reduce the marked left-ventricular hypertrophy (LVH) shown on the patient's last electrocardiogram (ECG). Which of the following drugs is least likely to produce the desired reduction in LVH?

- (a) aliskiren 150 mg daily
- (b) losartan 100 mg daily

- (c) irbesartan 150 mg daily
- (d) hydrochlorothiazide 25 mg daily

7. A 78-year-old African American female presents to the primary care clinic for a refill of hydrochlorothiazide 25 mg daily and amlodipine 10 mg daily. Three months ago, she was hospitalized following an episode of atrial fibrillation and now takes warfarin 2.5 mg daily (most recent international normalized ratio [INR] 2.9). Serial blood pressures at this visit (taken at 2 min intervals) were 159/93, 150/94, and 152/93 mm Hg. Her physician would like to start aliskiren 150 mg daily. Based on current clinical evidence, aliskiren:

- (a) produces a clinically significant increase in INR.
- (b) increases warfarin metabolism but has no significant effect on INR.
- (c) reduces warfarin absorption but has no significant effect on INR.
- (d) produces a clinically significant reduction in INR.

8. Like other inhibitors of the RAS, aliskiren is contraindicated in patients with severe renal dysfunction. Which of the following describes the correct physiologic basis of this contraindication?

- (a) RAS inhibitors block angiotensin II-mediated vasoconstriction in the efferent renal arteriole, leading to reduced glomerular filtration.
- (b) RAS inhibitors are moderately nephrotoxic, leading to severe interstitial nephritis with prolonged use.
- (c) RAS inhibitors accumulate in the renal tubules, leading to acute tubular necrosis.
- (d) RAS inhibitors are highly protein bound, leading to reduced renal perfusion in patients with severe renal dysfunction.

9. A 66-year-old male presents to the clinic for hypertension follow-up. Eight weeks ago, he was started on aliskiren 150 mg daily; his blood pressure at that time was 158/98 mm Hg. After 4 weeks of treatment, his blood pressure had decreased to 148/92 mm Hg and the dosage was increased to 300 mg daily. The patient's blood pressure today is 144/90 mm Hg, and he reports no symptoms of adverse events. Based on current evidence, should the dosage be increased at this time?

- (a) Aliskiren has not been studied at daily doses exceeding 300 mg/day.
- (b) Aliskiren 600 mg daily appears no more efficacious than daily doses of 300 mg.
- (c) Aliskiren 600 mg daily appears more efficacious than daily doses of 300 mg, but has been associated with significant hypotension.
- (d) Aliskiren 600 mg daily appears more efficacious than daily doses of 300 mg and is not associated with an increased rate of adverse events.

10. A 57-year-old female is diagnosed with hypertension, type 2 diabetes, chronic obstructive pulmonary disease, hyperlipidemia, and idiopathic dilated cardiomyopathy. Her current medications include lisinopril 20 mg/day, amlodipine 10 mg/day, simvastatin 40 mg/day, ezetimibe 10 mg/day, pioglitazone 30 mg/day, digoxin 0.125 µg/day, and ipratropium/albuterol inhaler 2 puffs 4 times daily as needed. Which of the following statements is the most accurate description of potential drug interactions with aliskiren?
- Aliskiren may reduce pioglitazone metabolism via CYP2C8 inhibition.
 - Aliskiren may reduce simvastatin metabolism via CYP3A4 inhibition.
 - Aliskiren may increase the risk of hyperkalemia via combined RAS blockade with lisinopril.
 - Aliskiren may reduce serum digoxin concentration through a P-glycoprotein interaction.
11. A 44-year-old male with newly diagnosed stage I hypertension is prescribed aliskiren 150 mg/day. Which of the following is the most accurate description of potential adverse reactions with aliskiren?
- Aliskiren inhibition of angiotensin II activity may increase levels of bradykinin and substance P, resulting in increased cough response.
 - There have been no adverse drug reactions reported in clinical trials with daily aliskiren doses of 150–300 mg.
 - The most common adverse reactions in clinical trials with aliskiren were headache, dizziness, and diarrhea.
 - In rare cases, aliskiren has caused severe abdominal cramping associated with alcohol ingestion.
12. Which of the following statements concerning aliskiren use in pediatric populations is *true*?
- Aliskiren has not been studied in patients less than 18 years old.
 - Pediatric studies with aliskiren were primarily short term (<8 wk).
 - Patients aged 12–17 years should initiate therapy with a reduced aliskiren dose (75 mg/day).
 - Daily aliskiren doses greater than 1 mg/kg were associated with increased adverse events in pediatric clinical trials.
13. Which of the following endpoints has been demonstrated in clinical trials?
- Aliskiren reduces the risk of myocardial infarction in patients with hypertension.
 - Aliskiren reduces the risk of microalbuminuria in patients with type 2 diabetes mellitus.
 - Aliskiren improves cardiac index in patients with left-ventricular systolic dysfunction.
 - Aliskiren produces blood pressure reductions comparable with those achieved with therapeutic doses of irbesartan.
14. Abstract reports describe the use of aliskiren for the treatment of hypertension in which of the following patient populations?
- hypertensive patients with type 2 diabetes mellitus
 - hypertensive patients uncontrolled with amlodipine monotherapy
 - hypertensive patients with left-ventricular systolic dysfunction
 - hypertensive patients unable to tolerate traditional doses of ACE inhibitors
15. A 30-year-old male with stage I hypertension was started on aliskiren monotherapy one month ago. He received a 30 day supply of aliskiren sample from your clinic, but returns to the clinic today because his insurance will not cover the drug. He is concerned about adverse reactions and reports no problems during this treatment period. Which antihypertensive is most similar to aliskiren in terms of patient tolerability?
- irbesartan 150 mg/day
 - captopril 50 mg 3 times daily
 - controlled release diltiazem 120 mg/day
 - metoprolol 100 mg twice daily