Asthma: Oral Therapies

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The treatment of asthma often requires multifocal modulation of disease pathways. As such, oral medications that are considered alternative treatments of asthma include: the leukotriene receptor antagonists (LTRA), montelukast (Singulair®) and zafirlukast (Accolate®), the leukotriene synthesis inhibitor, zileuton (Zyflo CR®), and the oral bronchodilator, theophylline.

Use of these oral medications in adults is typically limited to step 2, 3, and 4 as long-term control medications for persistent asthma. In step 2 care, although the preferred medication is low-dose inhaled corticosteroids (ICS), the LTRA class of medications and theophylline alone are appropriate alternatives. Step 3 care typically requires low-dose ICS in combination with a long-acting β-2 agonist (LABA) or medium-dose ICS alone. Suitable alternatives include low-dose ICS in combination with a LTRA, theophylline, or zileuton. Finally, in step 4 care, medium-dose ICS plus a LABA is preferred, but medium-dose ICS plus a LTRA, theophylline, or zileuton can be considered alternatives.

The LTRA medications montelukast and zafirlukast work to mitigate leukotriene-associated asthma symptoms including airway edema, smooth muscle contraction, and airway remodeling associated with inflammation. These medications have been well-studied in the asthma population, and have strong evidence supporting their use. The use of LTRA medications alone in step 2 care and in combination with low-dose ICS in step 3 care is considered to be level ‘A’ evidence and is supported by several randomized-controlled trials. Their use in combination with medium-dose ICS in step 4 care is not as well-documented, but is still recommended as level ‘B’ evidence. In studies of effectiveness in combination with ICS,LTRAs were found to increase mean morning forced expiratory volume in 1 second (FEV₁), decrease excessive airway narrowing, and improve overall control of asthma symptoms.

Generally, these medications are well-tolerated, although 10-15% of patients using zafirlukast report headache. Other adverse effects associated with both medications include elevations in liver function tests (LFTs), dizziness, fatigue, and nasal congestion. Both medications are metabolized by the cytochrome-P450 system, but present no therapy-modifying drug interactions. Sustained-release theophylline results in bronchodilation through increased tissue concentrations of cyclic-AMP and has been shown to have mild anti-inflammatory properties. The use of theophylline alone in step 2 care, in combination with low-dose ICS in step 3 care, and in combination with medium-dose ICS in step 4 care is considered an appropriate alternative to preferred treatments, but is classified as level ‘B’ evidence.

Overall, theophylline is considered efficacious, particularly in combination with ICS. However, while its utilization is supported by several randomized, placebo controlled trials, theophylline’s use is limited as it is considered a narrow-therapeutic index medication requiring specialized dosing, therapeutic monitoring, and good patient compliance. Typically, serum theophylline levels of 10-15 mcg/mL are considered therapeutic, while values greater than 20 mcg/mL are usually harmful. Common symptoms associated with theophylline toxicity include tachycardia, headache, restlessness, nausea, vomiting, tremor, and excess diuresis. It is recommended that serum drug levels be monitored prior to making a dosage adjustment or in the presence of signs and symptoms of toxicity or treatment failure. Theophylline is hepatically metabolized, and as such, its efficacy should be monitored when the patient is concurrently prescribed barbiturates, carbamazepine, and erythromycin.
P & T Committee Meeting Update

The P&T Committee met for its bimonthly business meeting on May 19, 2011. Highlights of this meeting include the following.

The Department of Health is undergoing reorganization. There will be no impact on the DUR program.

The Gilenya criteria was updated as follows:

**Gilenya:** Trial and failure of interferon and Copaxone.

The following prior authorization criteria were approved:

**Seroquel:** Prior authorization will be required for use of doses at or below 100 mg for greater than 30 days.

**Daliresp:** Prior authorization will be required. Concurrent use of a long-acting anti-muscarinic required.

**Horizant:** Two month trial and failure of dopamine agonists and gabapentin prior to approval. Diagnosis of restless leg syndrome required. Dose will be limited to 600 mg per day.

**Virasal:** Trial and failure of two over-the-counter salicylic acid products.

The Committee reviewed DERP reports for the following classes:

- **Omega-3 and DHA prenatal vitamins:** Non-preferred. Allowed for patients at high risk for pre-term labor.

The Wyoming Board of Medicine, the Wyoming Drug Utilization Review Program, Wyoming Workers’ Safety and Compensation Division, and Federation of State Medical Boards (FSMB) are co-sponsors in pain management education in Wyoming. In March 2011, a copy of Responsible Opioid Prescribing: A Physician’s Guide by Scott Fishman, M.D., Chief of the Division of Pain Medicine and Professor of Anesthesiology at the University of California, Davis was provided, free of charge, to Wyoming physicians. The book is published by the FSMB.

These agencies recognize that principles of quality medical practice require that patients have access to appropriate and effective pain relief. Wyoming physicians are encouraged to give this short but very informative book their full attention.

The Physician’s Guide is accredited for continuing medical education (CME) credit. This program is jointly sponsored by the University of Wisconsin School of Medicine and Public Health, the Alliance of State Pain Initiatives, and the Federation of State Medical Boards Foundation, and offers participants 7.25 AMA PRA Category 1 Credits™ for reading the book and successfully completing an on-line test on the material. The Wyoming Board of Medicine urges the physicians it licenses to participate in this program to earn some of the CME credits required for license renewal. Information on the CME, including how to register on-line and receive CME credit, is detailed on pages i-vii of the book.
Asthma: Oral Therapies, continued

The leukotriene synthesis inhibitor, zileuton, inhibits the enzyme 5-lipoxygenase that prevents synthesis of cysteinyl leukotrienes and leukotriene B4 thereby reducing airway inflammation in asthma. Zileuton is a relatively new medication in the treatment of asthma that has not been well-studied in combination with other asthma medications, such as ICS. While zileuton is offered as an alternative treatment in Step 3 and 4 care in combination with low- and medium-dose ICS, it’s use is considered level ‘D’ evidence. Another limitation of zileuton is an elevation in LFTs in 2-3% of patients. While this elevation has not been linked to irreversible liver injury, it is still recommended that LFTs are checked within the first 3 months of zileuton therapy and therapy discontinued if levels rise to more than 1.5-2 times upper limit of normal. Additionally, active liver disease or LFTs greater than 3 times the upper limit of normal is considered a contraindication for zileuton use. Zileuton has a relatively clean drug interaction profile, although it may increase serum concentrations of warfarin, theophylline, and propranolol.

The LTRAs, theophylline, and zileuton all present different treatment options for patients with asthma. While the medications are not considered preferred care, some patients may benefit from their use. Overall, these medications are considered safe and effective. Currently, the use of these oral medications in adults is typically limited to step 2, 3, and 4 care of persistent asthma as long-term control medications. With time, the role of these medications in the treatment of asthma may expand and evolve.

References

4. Ducharme F, Di Salvio F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children (review). The Cochrane Database of Systematic Reviews. 2008;4:CD002314.
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