ISSUE - 2 | VOLUME - 1 | 2011

LECOM Point

WELCOME TO LECOM POINT, ISSUE 2, VOLUME 1. A DRUG INFORMATION SOURCE THAT IS DIRECT AND TO THE POINT

LECOM CDIR 2.0

The LECOM Center for Drug Information and Research (CDIR) was established with a mission to provide students, faculty, preceptors, and the public with timely, independent, best-evidence analysis and commentary on pharmaceuticals and healthcare policy as it relates to pharmaceuticals. Our aim is to take advantage of our virtual world and develop an online drug resource accessible to anyone via the Internet.

For the LECOM community, the CDIR acts as a direct resource for our medical, pharmacy and dental providers, faculty and preceptors who need answers to specific drug information questions.

The CDIR website is being updated with new content frequently. Users can sign-up for our Twitter updates and RSS feeds. As we work to develop our virtual presence, the CDIR team will provide this newsletter as a service to the entire LECOM family. Feel free to contact us with drug information questions, general questions or comments at cdir@lecom.edu.

Benlysta, a new drug approved for lupus treatment

The U.S. FDA recently approved the first new drug for systemic lupus erythematosus (SLE) since 1955.[1]

Belimumab (Benlysta), is produced jointly by Human Genome Sciences, Inc and GlaxoSmithKline. It is a human, IgG, monoclonal antibody directed at B lymphocyte stimulator protein (BLyS).[2] BLyS is a member of the tumor necrosis factor (TNF) cytokine superfamily responsible for B lymphocyte homeostasis.[3]

In patients with lupus, BLyS levels elevate leading to abnormal B cell activation and creation of abnormal B cells. These B cells are thought to play a role in the development of lupus autoantibodies.[4] Animal studies have shown an increased incidence of SLE in mice that overexpress BLyS as well as clinical improvements in SLE mice when treated with a BLyS antagonist.[5]

Belimumab is designed to block BLyS, decreasing the amount of abnormal B cells. It is approved for use in antibody-positive patients currently taking standard therapy for lupus such as prednisone, NSAIDs, immunosuppressants or antimalarial medications.[2] Dosing is by IV infusion with 10 mg/kg every 2 weeks for three doses, then every four weeks thereafter.

Continues on Page 2

Continued from Page 1—Benlysta

Infusion (17%), hypersensitivity (13%) and anaphylactic (0.6%) reactions occurred in clinical trial patients with symptoms of headache, nausea, urticaria and dyspnea.[2] Infusion centers will need to be prepared for treatment of anaphylaxis when administering belimumab.

Approval for belimumab was based on data from three clinical trials, including BLISS-52 which showed response after 52 weeks of treatment.[6] Patients reported decrease in disease activity scores and increased time to flares with belimumab. Nearly 30% of patients were able to reduce their prednisone dose by the end of the 52 weeks of treatment.[6]

Clinical trials with 10 mg/kg belimumab dosing showed statistically significant improvement or stability of symptoms in nearly 60% of SLE patients.[2] No drug interactions have been identified. Safety during pregnancy and breastfeeding has also not been established.[2] The number of patients who would need to be treated with belimumab in order to improve disease activity is approximately 7 to 11.[7]

However, based on data from multiple trials, all-cause mortality with belimumab was slightly higher than placebo in clinical trials with a rate of 0.9%.[2] Experts suggest that for every 30 to 50 patients who note disease improvement with belimumab, there will be one death. Infections such as respiratory and urinary tract were reported in 71% of patients.[2] Patients were also found to have higher incidence of depression during treatment with belimumab. Common side effects include nausea, diarrhea, fever and migraine.[2] A MedGuide outlining these serious side effects will be dispensed to patients with their prescription.

African-Americans, a population with a high incidence of lupus, were found to have a lack of symptomatic improvement with belimumab as compared to placebo. Also, though the length of time to lupus flare improved, patients did not experience any fewer severe lupus flares while on belimumab.[2]

Cost will likely be an issue. The estimated amount per 400 mg vial is $1,477 with an approximate annual cost of $35,000.[8]

Until more is known regarding long-term safety and outcome data, reserve belimumab for use as a last-line agent along with standard therapy to improve patients' symptoms.

References:

1. FDA approves Benlysta to treat lupus. U.S. Food and Drug Administration. March 9, 2011. Accessed March 14, 2011.
2. Benlysta Prescribing Information 2011. Accessed March 14, 2011.
3. Cancro, Michael. The BLyS family of ligands and receptors: an archetype for niche specific homeostatic regulation. Immunologic Reviews. 2004;202:237.
4. Cancro, Michael et al. The role of B lymphocyte stimulator (BLyS) in systemic lupus erythematosus. J Clin Invest. 2009 May 1; 119(5): 1066–1073.
5. Stohl, W. Systemic lupus erythematosus and its ABCs (APRIL/BLyS complexes). *Arthritis Research and Therapy* 2010;12(2):111. Epub 2010 Apr 22. Accessed April 2, 2011.
6. Navarra, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011; 377: 721–31.
7. FDA Center for Drug Evaluation and Research Arthritis Committee Meeting Minutes. November 16, 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM241198.pdf. Accessed April 7, 2011.
8. Belimumab for Systemic Lupus Erythematosus. American College of Rheumatology. http://www.rheumatology.org/publications/hotline/2011_03_15_belimumab.pdf Accessed April 5, 2011.

Potential Safety Signal Update

Last quarter, the CDIR Newsletter gave a brief introduction to the Adverse Event Reporting System (AERS) database.[1] This will be the first quarter that we will be highlighting important ***potential*** safety signals from the Food and Drug Administration's (FDA). Although it is important to note that the FDA has identified a potential safety issues, it does not mean that the FDA has identified a causal relationship between the drug and the listed risk.[2] Despite this, we feel that these are important signals to watch for as potential safety signals can lead to important labeling changes.

There are a couple of interesting facts about the latest quarterly report.[3] Dronedarone was listed with a potential signal of renal impairment, and renal failure. Dronedarone has been linked to a potential safety signal in every quarter of 2010, and now the first quarter of 2011. Over the last four quarters dronedarone has been tagged for liver failure and congestive heart failure (which included an updated labeling approved in February),[4,5] a drug interaction with warfarin (which included an updated labeling approved in March),[6] and Torsade de Pointes that the FDA is still evaluating.[7] The latest signal of renal impairment, and renal failure may not be a surprise to some as the product can cause an increase in serum creatinine (already documented in the latest labeling).[8] Other note worthy signals included a signal of Sweet's syndrome with azathioprine which resulted in a labeling change that was updated in May. Additionally, the following are a few signals the FDA is still evaluating including, pseudotumor cerebri with quinolone products, hypersensitivity reactions due to prasugrel usage, and hypogammaglobulinemia from rituximab. The full table of the latest quarter report evaluated by the FDA can be located here….January - March 2011.

We feel that keeping abreast of all adverse drug reactions is of vast importance to weigh the risk/benefit of any drug. The top 200 drugs dispensed in the United States have an average of 105 adverse reactions and recognizing them is a fundamental key to calculating an incidence.[9] As always, if an adverse reaction does occur please report it to the FDA here.

References

New Recommendations for Statin Therapy

Recent changes to simvastatin dosing recommendations

The U.S. Food and Drug Administration (FDA) has recently updated the prescribing information for simvastatin.[1] There has been concern regarding the efficacy and safety of high-dose (80mg) simvastatin with some healthcare professionals questioning whether the benefit outweighed the additional risks of myopathy and rhabdomyolysis. The change in prescribing information is in response to recently published trial conducted by the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group.[2] The study was a double-blind randomized trial comparing high-dose (80mg) and low-dose (20mg) simvastatin daily. Upon completion, no significant difference was found between the two doses in regards to reduction of vascular events, but a significantly greater rate of myopathy was reported in the high-dose group.[2]

FDA is recommending use of the 80mg dose only in patients who have been taking the dose for 12 months or more without evidence of myopathy.[1] Additionally, FDA recommends not starting simvastatin 80mg in new patients, including patients already taking lower doses of the drug.[1] These recommendations will also include label changes for Vytorin® and Simcor®. There will also be label changes for simvastatin regarding contraindications and dose limitations when used concomitantly with certain medications.[1]

What does this mean for Health Care Professionals?

Practitioners may be asking what to do for patients with dyslipidemia in light of the recent changes. Keep in mind that this change does not apply to patients that have been taking simvastatin 80mg for 12 months or more without evidence of muscle toxicity. Should you have a patient who is above their LDL goal and is currently taking simvastatin 40mg, do not increase the dose to 80mg as the risk of myopathy increases with a potential further LDL reduction of only about 6%.[3] Instead, recommend switching to a more potent statin such as rosuvastatin or atorvastatin.[4] Remember to use caution when prescribing medications that can increase simvastatin levels. With the new label changes, simvastatin use is contraindicated with strong 3A4 inhibitors such as gemfibrozil, cyclosporine, and danazol. Doses of 10mg should not be exceeded if using amiodarone, verapamil, or diltiazem and doses of 20mg should not be exceeded if using amlodipine or ranolazine.[4]

Detailed information on relative LDL-lowering efficacy of statin and statin-based therapies and dosing limitations when taking simvastatin with interacting medications can be found at http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm.

References:

1. U.S. Food and Drug Administration. Zocor (simvastatin): Label change – New restrictions, contraindications, and dose limitations [Internet]. [updated 2011 Jun 8; cited 2011 Jun 30]. Available from http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258384.htm
2. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH) collaborative group. Intensive lowering of LDL cholesterol with 80mg versus 20mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomized trial. *Lancet* 2010;376(9753):1658-69
3. Zocor (simvastatin) Professional Product Label. At: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019766s076lbl.pdf. Accessed: June 30, 2011.
4. FDA Drug Safety Communication U.S. Food and Drug Administration. FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury [Internet]. [updated 2011 Jun 9; cited 2011 Jun 30]. Available from http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm

New Medication Approvals

Dificid (fidaxomicin)

On May 27, 2011 the FDA announced approval for Dificid (fidaxomicin), a new macrolide antibiotic for the treatment of *Clostridium difficile* (*C. difficile)* [1] .

In a head-to-head, non-inferiority trial with oral vancomycin (125 mg) four times a day for ten days, Dificid was found to be non-inferior to vancomycin. This study also concluded that Dificid was superior to vancomycin at sustained clinical response at the end of a 4 week follow-up [2], [3].

The treatment course of Dificid is one (1) 200 mg tablet by mouth twice a day for ten days [1]. The main side effects of Dificid are: nausea, vomiting and upset stomach. Dificid and its main metabolite are substrates for the PGP efflux transporter. Any inducers or inhibitors of PGP will affect the level of drug [4] . To prevent resistance emerging to Dificid it is only indicated when the infection has been proven or strongly suspected to be caused by *C. difficile* [1].

The new drug comes at a good time to offer clinicians an additional treatment option as a number of *C. difficile* strains with decreased susceptibility are emerging. Pelaez and colleagues reported that 26 of 415 tested strains of C. difficile had decreased susceptibility to metronidazole. Thirteen of the 415 tested isolates had decreased susceptibility to vancomycin. The highest rate of susceptibility came from HIV infected patients in both cases [5]

References

Rectiv (nitroglycerin) Ointment (0.4%) - formerly Cellegesic

Approved: June 21, 2011

Rectiv, approved on June 21, 2011 is the only FDA approved prescription medication for moderate to severe pain associated with anal fissures/ fistula [1]. It is expected to be available in the first quarter of 2012. Anal fissures have been associated with internal anal sphincter (IAS) hypertonia. These patients have been found to have low concentrations of nitric oxide in the IAS[2], [3]. Free radicals formed by Rectiv help to regulate the contractile state of smooth muscle. Intra-anal application of Rectiv reduces sphincter tone and resting intra-anal pressure [2],[3] One inch of Rectiv ointment is applied intra-anally every 12 hours for 3 weeks. Use of a finger covering is recommended[1]. Rectiv should be avoided in patients with severe anemia, glaucoma, hypotension, PDE5 inhibitor use, or increased intracranial pressure [1]. The most common side effect with anal administration of Rectiv is headaches, which can be treated with an analgesic [1].

Other conservative treatments may also be used concomitantly such as increased fiber intake, plenty of liquids, warm sitz bath, and bulk forming laxatives. A paper published in Colorectal Disease in 2008 stated the use of conservative treatments in addition to local anesthetics (hydrocortisone cream) and analgesics will heal a proportion of acute anal fissures [2],[3]. Reoccurrence rates were reduced from 68% to16% at 1 year following continued conservative management [3]. Medical management of acute anal fissure should be treated with a combination of conservative treatments and topical diltiazem 2% cream [3]. Diltiazem cream is helpful in the treatment of anal fissures because it blocks calcium ion entry in vascular smooth muscle causing muscle relaxation and vascular dilation [3]. Chronic fissures should be managed with diltiazem 2% cream topically twice a day for 6-8 weeks [3]. However, diltiazem is not currently approved for the treatment of anal fissures/fistula. Rectiv, being the first approved medication for this indication will aid in relief to these patients.

References

Overtime….

The National Physicians Alliance (NPA) has published recommendations for avoidance of the top 5 wastes of healthcare dollars in family medicine, internal medicine and pediatrics. Formed in 2005, the NPA is composed of 22,000 members in the United States. Their goal is to promote high-quality, evidence-based, and cost-effective healthcare for everyone.

The top five lists were developed through working groups composed of NPA members in each specialty. Surveys aimed at defining the top 5 "evidence-based, quality-improving and resource-sparing activities" that could be performed by physicians in their own practices. Eighty-three physicians completed an initial round of field-testing while 172 finished a second round of testing. Recommendations are as follows:

Family Medicine Top 5

1. No imaging for low back pain in first six weeks without presence of warning signs such as neurologic deficits.
2. No antiobiotics for acute sinusitis unless symptoms have been present for one week or have worsened after initially improving.
3. No annual cardiac screening, including ECG, in asymptomatic, low-risk patients.
4. No PAP tests on women < 21 or post-hysterectomy for benign disease.
5. No DeXA to screen for osteoporosis in women < 65 or men < 70 without risk factors.

Internal Medicine Top 5

1. No imaging for low back pain in first six weeks without presence of warning signs such as neurologic deficits.
2. No screening chemistry panels or U/A in asymptomatic, healthy adults.
3. No annual cardiac screening, including ECG, in asymptomatic, low-risk patients.
4. Generic statins are preferred over brand name statins for initial treatment of hyperlipidemia.
5. No DeXA to screen for osteoporosis in women < 65 or men < 70 without risk factors.

Pediatrics Top 5

1. No antibiotics for pharyngitis unless strep positive.
2. No imaging for minor head injuries unless LOC or risk factors.
3. No early OME referrals in absence of physical abnormalities or developmental delay.
4. Don't recommend OTC cough and cold medications.
5. Use inhaled corticosteroids for asthma control.

Reference:
The Good Stewardship Working Group. The "Top 5" Lists in Primary Care: Meeting the Responsibility of Professionalism. *Archives of Internal Medicine*. 2011;171(15):1385-1390

LECOM Bradenton
5000 Lakewood Ranch Boulevard
Bradenton, FL 34211-4909

Main Phone No. 941-756-0690
Fax No. 941-782-5721

LECOM Erie
1858 West Grandview Boulevard
Erie, PA 16509-1025

Main Phone No. 814-866-6641
Fax No. 814-866-8123

LECOM SCHOOL OF PHARMACY
CENTER FOR DRUG INFORMATION AND RESEARCH

LECOM is a single school of pharmacy operating out of two locations situated 1,186 miles apart. Consistent with LECOM's core value of creating student-centered education, two distinct learning pathways are offered for the Pharm.D. degree providing students the option of choosing a pathway most suited to their learning needs. In Erie, PA, an accelerated three-year pathway is offered enabling students to complete the Pharm.D degree in three calendar years; in Bradenton, FL, a traditional four-year pathway is offered. Both curricula offer the same spectrum of didactic courses, credit hours, and experiential education and experiences. The full array of supporting services exists at both campuses. Physical facilities, at each campus, are state-of-the art and of sufficient volume to meet all educational and administrative functions.

Managing Editor: Melissa Murfin, PA-C, Pharm.D.

Drug Info Team: Ryan Wargo, Pharm.D.
Michael Mueller, Ph.D.
Melissa Murfin, PA-C, Pharm.D.
Alejandro Vazquez, Pharm.D.
Julie Wilkinson, Pharm.D., BCBS
Elliott Cook, Pharm.D., BCPS
Danielle Debias, Pharm.D.
Justin Scholl, Pharm.D.
Kathryn Samai, Pharm.D.